Open-heart surgery in congenital heart defects - Psychological adjustment in children and their parents

THESIS

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Contents

Summary

The event of open-heart surgery in children to correct for congenital heart defects is a source of great distress to the lives of affected families.

The present thesis focussed on the psychological adjustment and the quality of life in these children by systematically reviewing the empirical literature on long-term outcome in children following cardiopulmonary bypass surgery. Final conclusions of the review were hampered by the heterogeneity across methodological approaches. Nevertheless, the increased risk of psychological maladjustment, i.e. in particular for internalising behavioural difficulties, in this patient population emerged from the analysis.

A second emphasis of this thesis was placed on the assessment of surgery-related stress reactions in parents of children after open-heart surgery by physiological as well as psychological means. Findings were based on a prospective cohort study evaluating the diurnal cortisol secretion and posttraumatic stress symptoms in parents before and after surgery. Thus, significant changes in response to the surgical event were observed for either parameter. In addition, risk factors for posttraumatic stress symptoms were identified. Altogether, results of the study highlight the urgent need for systematic psychosocial support to families experiencing heart surgery in their child to benefit long-term parental well being, family functioning and finally, to ensure optimal development of the operated child.

Zusammenfassung

Die Operation am offenen Herzen bei Kindern mit einem kongenitalen Herzvitium stellt eine besondere Belastung im Leben betroffener Familien dar.

Diese Arbeit untersucht die psychische Anpassung und Lebensqualität bei jenen Kindern anhand eines systematischen Überblicks zu Langzeitstudien nach der Operation an der Herz-Lungenmaschine. Allgemeingültige Schlussfolgerungen des Reviews wurden durch die Vielfalt methodischer Ansätze erschwert. Dennoch zeigt die Analyse ein erhöhtes Risiko für psychische Fehlanpassung, insbesondere internalisierende Verhaltensschwierigkeiten, in dieser Patientenpopulation.

Ein zweiter Schwerpunkt dieser Arbeit beruht auf der Untersuchung von Stressreaktionen betroffener Eltern im Zusammenhang mit der Herzoperation ihres Kindes, operationalisiert durch physiologische und psychologische Merkmale. In einer prospektiven Kohortenstudie wurden die Cortisolsekretion und die posttraumatische Belastungssymptomatik vor und nach der Operation untersucht. Bedeutsame Veränderungen wurden für beide Parameter im Zusammenhang mit der Operation beobachtet. Des Weiteren wurden Risikofaktoren für das Entwickeln einer posttraumatischen Belastungssymptomatik identifiziert. Die Ergebnisse der Studie verdeutlichen den dringenden Bedarf für das Angebot einer systematischen psychosoziale Unterstützung, für einen Teil der betroffenen Familien, um das Wohl der Eltern, der Familie und nicht zuletzt die bestmögliche Entwicklung des operierten Kindes zu sichern.

Abbreviations

ACTH	Adrenocorticotropic hormone
AS	Aortic stenosis
ASD	Atrial septal defect
ASD	Acute stress disorder
AVSD	Atrioventricular septum defects
CHD	Congenital heart defect
CoA	Coarctation of the aorta
CRF	Corticotropin-releasing factor
CV	Coefficient of variation
DILV/ DORV	Double inlet left/ right ventricle(DILV/DIRV)
DORV	Double outlet right ventricle
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
HADS	Hospital Depression and Anxiety Inventory
HLHS	Hypoplastic left-heart syndrome
HPA axis	Hypothalamus-pituitary adrenal axis
PA	Pulmonary atresia
PDA	Patent ductus arteriosus
PDS	Posttraumatic Diagnostic Scale
PS	Pulmonic stenosis
PTS	Posttraumatic Stress
PTSD	Posttraumatic Stress Disorder
QoL	Quality of life
SF-36	Short Form Health Survery-36
TAC	Truncus arteriosus communis
TF	Tetralogy of Fallot
TGA	Transposition of the great arteries
VSD	Ventricle septum defect

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1 Introduction

The current thesis aimed at evaluating whether open-heart surgery in infants and children with congenital heart defects affects the psychological long-term adjustment and the quality of life in these children. Although the surgical intervention may serve to correct or palliate the inborn malformation, side effects associated with surgery and residual or recurrent cardiac complications may compromise everyday life. A systematic review of the relevant literature of the last 15 years was conducted in order to derive conclusions as to the long-term adjustment in children with congenital heart defects after open-heart surgery.

As chronic paediatric illness may also affect parental well being and family functioning, a second focus of this thesis was placed on parental adjustment to open-heart surgery in their child. A prospective cohort study was conducted assessing surgery-related stress by means of physiological as well as psychological variables. Accordingly, the thesis contains the following formal structure:

Chapter 2 gives an overview of the anatomy and the functioning of the human heart highlighting the particularities of the intrauterine and the postnatal circulation. Selected defect are discussed with regard to their underlying pathophysiology and their associated consequences. Furthermore, an overview of genetic syndromes is given, which are often associated with inborn malformations of the heart. In **Chapter 3** the focus lies with the practical implications of living with a congenital heart defect for affected children and their parents. Psychological aspects relating to the event of open-heart surgery are discussed. The systematic review evaluating psychological adjustment and quality of life in children after open-heart surgery is presented in **Chapter 4**. The following chapter, **Chapter 5**, outlines fundamentals of the physiological stress response focussing on the stress hormone cortisol. As cortisol is a widely used parameter in stress research, empirical findings relating to acute, prolonged, and traumatic stress exposure are discussed. Based on the previous chapters, **Chapter 6** derives hypotheses regarding diurnal cortisol secretion in parents of children undergoing open-heart surgery as well as hypotheses regarding their psychological adjustment. **Chapter 7** presents the results of the empirical study which assessed diurnal cortisol secretion on parents before, during and some time after the day of open-heart surgery in their child. Study results regarding surgery-related posttraumatic stress in these parents are discussed in **Chapter 8**. Finally, **Chapter 9** considers the findings of this thesis and discusses their implications.

2 Congenital heart defects

The term ”congenital heart defect” (CHD) subsumes any malformation of the heart or the blood vessels near the heart, which exist by the time of birth. The terms ”congenital heart disease” or ”congenital heart disorder” have been used interchangeably in the literature. Prevalences between 2.1 and 12.3 CHD per 1,000 live births have been reported (Pradat, Francannet, Harris, & Robert, 2003; Botto, Correa, & Erickson, 2001; Samanek, 2000; Schötzau, Santen, Sauer, & Irl, 1997). This renders CHD a prominent inborn and chronic paediatric disorder. Defect severity ranges from small septal defects, which close spontaneously, to complex malformations of the heart causing an early death. More than a third of the affected children is born with ”critical heart disease” denoting malformations which acutely threaten life and necessitate palliative or corrective surgery in early life (Marino, Bird, & Wernovsky, 2001; Samanek, 2000). As medical advances in surgery and supportive care techniques have significantly reduced mortality, the population of CHD survivors has considerably increased during the last decade (Allen, Gauvreau, Bloom, & Jenkins, 2003; Boneva et al., 2001). As a result, issues of long-term medical care, neurological and cognitive development, psychobehavioural adjustment, and quality of life for children with CHD and their families have been the subjects of much current research.

In order to understand the underlying pathophysiology of the various CHD diagnoses and their medical consequences, anatomy and functioning of the human heart are outlined briefly in the following section. Particularities of intrauterine and postnatal circulation are highlighted before an overview of the most common heart defects is given. As the event of open-heart surgery is of particular relevance for this thesis, associated developments, techniques and risks are introduced. Lastly, genetic syndromes, which are often accompanied by heart defects, are described. The aim is not to educate the unfamiliar reader in anatomical and medical detail but to provide some basic insight. This may enhance the understanding of the potential consequences of CHD and its surgical repair for the affected child and the parents, as well as for their interaction.

2.1 The human heart before and after birth

The human heart, a muscular pump, continuously pumps blood through the circulatory system by repeated rhythmic contractions. Its anatomy is depicted in figure 2.1 and will be introduced by sketching the heart's functioning. Essentially the heart consists of four chambers, the *left* and the *right atrium*, and the *left* and the *right ventricle*. The left and right sides of the heart are separated via the *septum*. *Valves* between atria and ventricles enable a unidirectional blood flow from the atrium to the ventricle. Ascending and descending vessels link the heart with the body and the lungs. Here valves also allow for a unidirectional blood flow. Thus, one differentiates between *body* and *lung circuit*, which operate in serial order: Deoxygenated blood from the body enters the right atrium via the *superior* and the *inferior vena cava* and flows through the *tricuspid valve* into the right ventricle. Contraction of the ventricle causes the tricuspid valve to shut and forces the *pulmonary valve* to open. This way blood flows into the *pulmonary artery* and from there into the lungs, where it takes in oxygen and releases carbon dioxide (lung circuit). The *pulmonary veins* carry the oxygenated blood to the left atrium of the heart. Then the blood flows through the *mitral valve* into the left ventricle. Contraction of the left ventricle closes the mitral valve and opens the *aortic valve* at the entry to the *aorta* (body circuit). From there oxygen-rich blood enters the systemic circulation (Marieb, 2001).

The intrauterine circulatory system in the foetus differs from the circulation described above (Artman, Mahony, & Teitel, 2002). Here circulation works in parallel circuits. As the foetus does not as yet use its lungs, oxygen and nutrients are obtained from the mother's placenta via the umbilical cord. Other distinct anatomical features are the open *ductus arteriosus* and the open *foramen ovale*. The ductus arteriosus is a connection between the pulmonary artery and the aorta descendens directing most of the blood away from pulmonary circulation. The foramen ovale denotes an opening between the right and left atrium. This opening causes most of the blood to flow from the right into the left atrium, then into the left ventricle and via the aorta into the body.

The characteristics of foetal haemodynamics enable the intrauterine circulation to function with a significant proportion of congenital heart malformations. If they do not, the foetus is aborted. Even a single ventricular system can suffice for a foetus to develop and it is only after the child is born that clinical symptoms arise. Immediately after birth the cardiovascular system and blood flow pattern change dramatically. The newborn must adapt to a new circulation, where oxygen exchange occurs in the lungs rather than in the placenta. Artman summarised three critical adaptations occurring during the first few minutes of postnatal life (Artman et al., 2002):

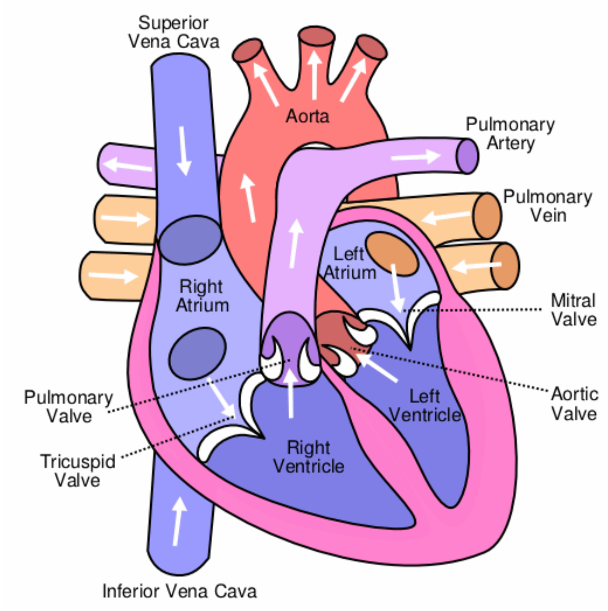

Figure 2.1: Gross anatomy of the human heart (Wapcaplet, 2006)

- a circa 20-fold increase in pulmonary blood flow compared to intrauterine blood flow
- significant alterations in central blood flow patterns from parallel to serial circulation as foramen ovale and ductus arteriosus close
- a great increase in ventricular output in order to meet the growing energy requirements

With the first breath, more blood moves from the right atrium to the right ventricle and into the pulmonary arteries. Less blood flows through the foramen ovale to the left atrium. In contrast, more blood travels via the pulmonary artery to the lungs and through the pulmonary veins to the left atrium. This increases the pressure there. The increased left atrial pressure and decreased right atrial pressure cause the foramen ovale to close. The ductus arteriosus normally closes within a few days of birth due to muscular cell contraction. For a comprehensive overview of the foetal circulation and early postnatal circulatory changes see Arman (Artman et al., 2002) or Polin (Polin & Fox, 1992).

As already stated, the clinical manifestations of CHD develop after birth. Depending on type and size of malformation they may become apparent immediately, during the first months, during childhood or later in life. In the following some of the most prevalent CHD are briefly described by their anatomical characteristics as well as by their functional pathology.

2.2 Main diagnoses of congenital heart defects

Several approaches exist to categorise the numerous heart defects. One way is to globally differentiate between *cyanotic* and *acyanotic* CHD. About 20-30% of all defects are cyanotic heart defects resulting from a right-to-left shunt, which causes oxygen-poor blood to enter the body circulation. Cyanotic children are recognised by the characteristical blue discoloration of their skin. In contrast, acyanotic children do not suffer from cyanosis. Here either a left-right shunt or no shunt is present.

Another approach classifies defects according to the underlying structural characteristics. For the current purpose, we shall distinguish between defects arising from deficient partition, from obstruction, from transposition of ascending or descending vessels, and from univentricular anatomy. These defects may occur in an isolated way, combined or as elements in more complex CHD. In the following a selection of heart defects will be discussed.

Details of the particular defects have been extracted from the *www.emedicine.com* webpage, a site to which medical experts contribute and update their knowledge on a regular basis. The individual authors are denoted at the end of each paragraph. Generally the cardiology text books by Keck & Hausdorf (Keck & Hausdorf, 2004) and Mewis (Mewis, Riessen, & Spyridopoulos, 2002) were consulted.

2.2.1 Deficient partition and septal defects

Ventricle septum defect (VSD) A VSD, one of the most common CHD, is characterised by a hole in the dividing wall between the lower chambers of the heart, the left and the right ventricles. Timing and magnitude of clinical manifestation of symptoms depend on the size of a defect and the extent of left-to-right shunting. Small defects do not change haemodynamic conditions, however in a moderate-sized VSD about a third of oxygen-enriched blood passes from the left ventricle through the hole back into the right ventricle, where it mixes with oxygen-poor blood. The blood volume within the right heart increases and causes heightened pressure in blood vessels in the lung as it passes through the pulmonary artery into the lungs. If left untreated, a VSD can cause permanent damage to vessels in the lungs. Further, it can cause heart insufficiency with the associated symptoms of rapid breathing, excessive sweating, and fatigue when feeding. Large defects may even lead to a reversal of the shunt flow and thus cause cyanosis. Unless spontaneous closure occurs, the VSD is surgically closed in infancy or in early childhood by means of open-heart surgery. In about half of the cases a VSD co-occurs with other heart defects (Anbumani, Srinivasan, Ramaswamy, Srinivasan, & Natesan, 2004).

Patent ductus arteriosus (PDA) The ductus arteriosus, a connection between pulmonary artery and aorta in the foetus, normally closes spontaneously a few days after birth. If it fails to close, it is called a persisting or patent ductus arteriosus. This way it produces a left-to-right shunt, where blood from systemic circulation flows back into lung circulation via the aorta. Constant pulmonary overcirculation can lead to left atrial and ventricular enlargement. Depending on the size of the PDA, symptoms may be experienced or not. If the ductus is large, frequent respiratory infections, heart insufficiency, even cardiac failure may occur. The risk of developing endocarditis, an inflammation of the endocard, is particularly high. Small PDAs in infants can be closed by pharmacological means, otherwise interventional heart catheterisation or cardiac surgery is applied. In co-occurrence with another heart defect, e.g. in case of the transposition of the great arteries, the PDA may be artificially kept open by using prostaglandin to compensate for associated malformations until they are corrected surgically (Neish, 2004).

Atrial septal defect (ASD) An ASD is characterized by a hole in the dividing wall between right and left atrium. As a result oxygen-rich blood leaks from the left atrium back into the right atrium. Hence blood, which has already been enriched with oxygen, is pumped back into the lungs for further oxygen enrichment. Depending on the location of the hole, four basic types of ASD are distinguished. They occur alone or in combination with other defects. Clinical effects of ASD relate to the degree of left-right shunting. Yet they do not occur until late childhood, adolescence or even adulthood. The manifestation of symptoms in childhood is often subtle and non-specific. Often the diagnosis is only made accidentally by auscultation of a heart murmur. Some children, however, may experience poor weight gain, stunted growth, and exertional dyspnea. Frequent upper respiratory tract infections are rather typical. Closure of an ASD by surgery or catheterisation is necessary to prevent late complications, such as arrhythmias, heart insufficiency or pulmonary hypertension (King & Thapar, 2003).

Atrioventricular septum defects (AVSD) AVSD, also called endocardial cushion defect or atrioventricular canal defect, stands for various defects involving the atrioventricular valves (tricuspid and mitral valve), and septal tissue above and/or below the atrioventricular level. A canal defect may be classified as partial or complete. In a partial canal defect, either the atrial or the ventricular part of the septum is affected. A complete AVSD, which is more common, means that the hole is located where atrial and ventricular parts of the septum normally meet. Depending on how much blood flows through the VSD and how much blood flows back from the AV valves, symptoms develop early. In the worst case an infant with a complete AVSD may develop congestive heart failure, tachypnea, excessive sweating, show poor feeding habits, and fail to thrive. Under less severe circumstances patients may be asymptomatic until the second or third decade of their life. A complete AVSD is surgically treated. AVSD is the most common heart defect in Trisomy 21 (McConell & Scheitler, 2004).

2.2.2 Obstructive defects

Pulmonic stenosis (PS) PS generally refers to an anatomical obstruction in the blood flow from the right ventricle to the pulmonary artery. It can occur at valvular, subvalvular, or at more peripheral levels. Valvular PS is a narrowing of the pulmonary valve, which opens to let blood flow from the right ventricle into the lungs. Due to this narrowing the right ventricle needs to pump harder in order to get blood past the blockage. The stenosis may be present in various degrees depending on the magnitude of the obstruction. No or few symptoms are exhibited in mild to moderate PS, whereas moderate to severe PS can lead to fatigue, shortness of breath, heavy or rapid breathing, a rapid heart rate, and swellings in the periphery. In more severe PS the right ventricle becomes enlarged. Intervention by means of catheter (balloon valvuloplasty), or surgical repair with or without cardiopulmonary bypass, are applied. PS is involved in about half of the complex CHD (Saavedra & Cannistra, 2002).

Coarctation of the aorta (CoA) CoA involves a narrowing of the aortic isthmus, located at the passage from the aortic arch to the thoracic aorta. The blood flow to different parts of the body is restricted and a considerable afterload is imposed on the left ventricle. This may finally result in compensatory hypertrophy of the ventricle. Often, severe coarctation occurs at closure of the ductus arteriosus, caused by muscle fibres within the aorta. Affected children may experience poor feeding, fast breathing, lethargy, and signs of heart failure during the first weeks of life. Treatment by means of catheter (balloon aortoplasy) or different surgical techniques depend on age at presentation, anatomical characteristics and associated cardial anomalies. There is a heightened risk of recurrent coarctation, which necessitates a life-long medical follow up (Seib, 2002).

Aortic stenosis (AS) AS stands for a narrowing or an obstruction in the aortic valve at sub- or supravalvular level. This way the valve is prevented from opening appropriately and thus, blood flow from the left ventricle to the aorta is blocked. As blood cannot be ejected properly into the aorta, pressure in the left ventricle increases, leading to a thickening of the ventricular walls. If left untreated, sustained pressure overload eventually leads to myocardial decompensation and congestive heart failure. Many patients are asymptomatic during childhood and the defect remains undetected until school age. Symptoms develop gradually and may include palpitations, fatigue, angina pectoris, shortness of breath and syncopes upon exertion. Surgical repair is delayed as long as possible in order to postpone late complications such as restenosis, or in the case of valve replacement, to await the heart's outgrowth. In infants with significant AS, congestive heart failure develops much faster during the first week of life necessitating emergency surgical intervention. AS is associated with the risk of sudden cardiac death (3-5 percent of patients), which is further increased under exertion. Depending on the degree of stenosis, sports activities may be contra-indicated (Balentine & Eisenhart, 2005).

2.2.3 Transposition of ascending and descending vessels

Transposition of the great arteries (TGA) TGA is one of the most common cyanotic CHD in the neonate. Here the great vessels are transposed as the aorta arises from the right and the pulmonary artery from the left ventricle. As a result pulmonary and systemic circulation operate in parallel. Oxygenated blood is recirculated to the lungs, while deoxygenated blood is pumped back into the body without having passed through the lungs. Unless there are anatomic sites which allow for the mixing of oxygen-enriched and oxygen-deficient blood (e.g. VSD, ASD, PDA) TGA is incompatible with life. In the absence of these defects, the ductus arteriosus can be kept open pharmacologically until surgery. The clinical course in TGA varies with the degree of intercirculatory mixing and the presence of anatomical lesions. Hence optimal timing of surgical repair also varies. TGA without other cardial anomalies are operated on within the first weeks of life. Here recent advances in surgical technique (arterial switch) have allowed for survival rates of over 90% (Charpie & Maher, 2004).

Double outlet right ventricle (DORV) Another malconnection of the great vessels is summarised under the diagnostic label of DORV. In DORV the pulmonary artery and the aorta arise completely or predominantly from the right ventricle. This "partial transposition" is always combined with a VSD, often with a PS or other ventricular anomalies. DORV does not comprise a single clinical entity, yet it results in various clinical presentations depending on the site of the VSD in relation to the great vessels and the severity of the PS. For example, children with DORV may experience symptoms similar to a VSD or a TGA. The surgical approach may include palliative and corrective surgical repair (Tarrago & Neish, 2004).

2.2.4 Tetralogy of Fallot - a combination of defects

So far examples of heart defects have been described that either involve deficient partition as in the septal defects, or obstructive lesions as in stenosis, or malalignment of the vessels. Tetralogy of Fallot (TF) can be seen as a combination of these defects. The most common cyanotic CHD is characterised by the following four anomalies:

- a subarortic VSD,
- a PS, determining the degree of right-to-left shunting,
- right ventricular hypertrophy, a thickening of ventricular walls and enlargement of the right ventricle, as a result of the PS,
- abnormal position of the aorta, exiting the heart from a position overriding the right and left ventricles rather than exiting it from the left ventricle.

The overriding aorta is supplied with blood from the left and the right ventricle, so oxygen-rich and oxygen-poor blood is pumped into the body. In addition the right-left shunt allows oxygen-deficient blood from the right ventricle to leak into the left ventricle, thus causing cyanosis. The degree of cyanosis depends on the gravity of the PS, as the stenosis determines how much blood passes through into the lungs. Infants with TF present with progressive cyanosis during the first months of life. Spasms at the outflow portion of the right ventricle can cause particularly severe episodes of cyanosis - called "tet spells". The TF infant shows poor feeding habits and often fails to gain weight. Children tire easily and begin to pant under exertion. They typically adopt a squatting position as this relieves the cyanosis. The chronic oxygen deficiency causes clubbed fingers and toes. Growth and development are delayed, particularly if the PS is severe. Optimally surgical repair is carried out during early childhood to close the VSD, remove the PS and ablate the thickening of the ventricular walls. In severe cases palliative shunt surgery is conducted to alleviate symptoms until corrective surgery can be done (Greenberg, 2004).

2.2.5 Univentricular circulation

Hypoplastic-left-heart syndrome (HLHS) The HLHS is an example of univentricular anatomy of the heart. Instead of two functioning ventricles only one ventricle is normally developed. In HLHS the left ventricle and the ascending aorta show marked underdevelopment. Mitral valve and aortic valve are atretic (blocked), hypoplastic or stenotic. Hence oxygenated blood cannot flow from the lungs to the left heart to be pumped into the systemic circulation. Alternatively it leaks through the atrial septum and mixes with de-oxygenated blood in the right atrium. The right ventricle then pumps the mixed blood into the pulmonary and systemic circulation. The latter is permitted by the open ductus arteriosus. As the ductus arteriosus closes a few days after birth the seemingly healthy infant rapidly develops symptoms of a cardiogenic shock including cyanosis, respiratory distress, paleness, lethargy, and anuria. Death ensues unless the ductus arteriosus is kept open by pharmacological means. Surgical reconstruction is aimed at separating the parallel functioning of lung and body circuitry into serial uni-ventricular circulation. This is achieved in three surgical stages; the first when the infant is a few weeks old, the second six months after stage one, and the third about twelve months after stage two. Due to advances in surgical technique mortality in HLHS has been greatly reduced (Turner & Forbes, 2003). Among the other univentricular heart defects are the **Double inlet left/right ventricle (DILV/ DIRV)** and the **Criss-cross heart**.

So far a range of CHD has been presented. Table 2.1 summarises the defects in order of their appearance in the text and gives estimates of their relative frequency. Besides diversity in occurrence of the individual defects, the term CHD clearly subsumes a wide range of malformations, which differ in anatomy, associated haemodynamics, severity, and time when symptoms manifest themselves. Hence the treatment approach differs greatly as to the type, timing and number of interventions. While some defects resolve themselves, as for instance in the case of spontaneous closure of a small VSD, other defects are treated by pharmacological means, e.g. a PDA. Yet other defects demand single or repeated corrective intervention either by catherisation, closed or open-heart surgery. The latter is either done with or without the use of the heart-lung machine. As the focus of this thesis lies on children who were operated on using the heart-lung machine, this type of surgical intervention will be looked at closer in the following section.

Table 2.1: Relative frequencies of major CHD diagnoses in live births in percent; [1](Botto et al., 2001), [2](Wren et al., 2000), [3](Hoffman & Kaplan, 2002).

Congenital heart defects	Atlanta 1968-1997[1]	United Kingdom 1985-1997[2]	mean across studies 1955-2000[3]
Ventricle septum defect (VSD)	26.8	42.6	37.2
Patent ductus arteriosus (PDA)	10.9	4.1	8.3
Atrial septum defect (ASD)	7.0	5.0	9.8
Atrioventricular septal defect (AVSD)	4.3	1.7	3.6
Pulmonic stenosis (PS)	16.2	6.0	7.6
Coarctation of the aorta (CoA)	4.7	4.3	4.3
Aortic stenosis (AS)	1.6	3.5	4.2
Transposition of the great arteries (TGA)	4.6	5.4	3.3
Double outlet right ventricle (DORV)	1.7	-	1.6
Tetralogy of Fallot (TF)	6.1	5.5	4.4
Hypoplastic left heart syndrome (HLHS)	3.3	2.6	2.8
other	12.8	19.3	12.9
overall prevalence of CHD/ 1000 live births	6.0	5.6	9.6

2.3 Open-heart surgery using the heart-lung machine

2.3.1 Historical developments

Before the 1950s intracardiac defects were approached only indirectly with closed cardiac surgery (Bolman & Black, 2003). However, in order to repair more complex defects, developments were needed that enabled surgery on the bloodless and motionless heart under preservation of vital functions. In 1953 John H. Gibbon was the first to successfully apply the idea of extracorporeal circuitry, when he operated on an 18-year-old patient with an ASD using the heart-lung machine (Pastuszko & Edie, 2004). One year later Walton Lillehei applied the cross circulation technique by means of a human being as biological oxygenator. This way TF, AVSD and VSD were successfully corrected (Gott, 2005). Nowadays, more than 50 years later, technical advancement of the heart-lung machine, surgical technique, the growing surgical expertise and a better understanding of the pathophysiology of CHD have contributed to a significant reduction in mortality (Elliott, 1999). Until the 1970s open-heart surgery was neither performed on children younger than two years of age, nor on children with a body weight of under 10 kg. The advances in paediatric cardiosurgery over the last decades have not only allowed open-heart surgery in these children, but also in high-risk infants, such as prematurely born and low-birth-weight children (T. Bove et al., 2004; Oppido et al., 2004). Moreover, complex malformations such as functionally univentricular hearts used to run a fatal course during the neonatal period or early infancy. In 1980, however, Norwood and colleagues reported the first successful palliative operation for an infant with an HLHS (Norwood, Kirklin, & Sanders, 1980). Operative mortality after intermediate and Fontan staging procedures in HLHS has been reported to be below 5% (E. L. Bove & Lloyd, 1996).

Although mortality rates in CHD have considerably decreased, many risk factors relating to short- and long-term morbidity following open-heart surgery remain. In particular the application of extracorporeal circuitry bears risks for organ functioning and development in the operated child. The following section briefly outlines machinery and functioning of the heart-lung machine before associated risk factors are discussed.

2.3.2 The heart-lung machinery and its associated risks

The heart-lung machine, also known as cardiopulmonary bypass or pump-oxygenator, functions as an artificial heart continuously pumping blood through the body. Meanwhile cardiac malformations can be surgically corrected. Before its initiation, a large drainage tube is placed into the right atrium. Another tube is placed into the arterial system, commonly into the aorta. Once the cannulas are placed, oxygen-poor blood is drained from the right atrium into a reservoir. From there it is pumped into the oxygenator, where the red blood cells are enriched with oxygen. The oxygen-enriched blood travels through a tube to the aorta and is subsequently pumped to the rest of the body tissue. This way the body's circulation can be kept up for hours, although machine time should be kept as short as possible. Various vital organ support methods exist, which accompany the cardiopulmonary bypass procedure. Most institutions use moderate hypothermia, a lowering of the body temperature, with full or reduced blood flow. The rationale behind the lowered body temperature is to reduce the metabolism and the oxygen consumption. This prevents damage to the central nervous system due to oxygen deficiency. In selected patients deep hypothermia (optimally between 14°C and 20°C) with circulatory arrest, or very reduced flow, is applied (Elliott, 1999).

Although much progress has been made with regard to the perfusion techniques of cardiopulmonary bypassing, and safety issues have constantly been addressed, risks as to morbidity and mortality in patients remain. For instance, the interaction between blood and the biocompatible surfaces of the heart-lung machine may cause systemic inflammatory responses which can, in the worst case, cause organ dysfunction (Murphy & Angelini, 2004). Also, capillary leak and consequently oedema are observed particularly in younger children and after long periods of bypassing (Elliott, 1999). Neurological abnormalities, such as neuromotor difficulties (Bellinger et al., 1999), impaired visuo-spatial skills (Bellinger, Bernstein, Kirkwood, Rappaport, & Newburger, 2003) or reduced cognitive functions (Wernovsky et al., 2000; Limperopoulos et al., 2002), have been observed in a proportion of children after open-heart surgery. Overall the incidence of reported neurological complications across institutions ranges from 1-25% (Jonas, 2000). Prolonged circulatory arrest and the duration of cardiopulmonary bypass may increase vulnerability to postoperative neurological impairment (Brown, Moody, Challa, Stump, & Hammon, 2000). On a cautious note: Although there is considerable support for the hypothesis that there is an increased risk of neurological abnormalities in CHD after open-heart surgery, evaluation of the neurodevelopmental outcome in these children is made difficult by the fact that a proportion of children lives with a genetic defect. Depending on the genetic syndrome present, developmental and cognitive delay may co-exist independent of the heart defect or the surgical intervention. The following section considers the genetic defects present in some CHD further.

2.4 Genetic syndromes in congenital heart defects

As the development of the human heart in the foetus is under the rule of numerous genes, genetic defects are sometimes accompanied by a maldevelopment of the heart. To illustrate this with an example, Trisomie 21 with its associated physical, developmental and behavioural characteristics is described.

Trisomy 21, also known as Down's Syndrome, is caused by trisomy of chromosome 21, as it has been tripled rather than doubled. It occurs in about 1 per 1,000 live births (Lai et al., 2002; Edmonds & James, 1993) and is highly dependent on maternal age (Sancken, Burfeind, & Engel, 2005). A meta-analysis by Bray and colleagues estimated a prevalence of 0.69/1,000 live births at a maternal age of 20 years rising to 38.9/1,000 at a maternal age of 45 years (Bray, Wright, Davies, & Hook, 1998).

In 40-50% of Trisomie 21 children a heart defect is present, predominantly an AVSD or a VSD (Freeman et al., 1998; Ferencz et al., 1989). Other non-cardiac congenital anomalies occur more frequently in children with Trisomy 21 than in non-Trisomy children. They often involve the gastrointestinal or the neurological system (Kallen, Mastroiacovo, & Robert, 1996). Acquired medical complications may arise for instance from frequent infectious disease (Hilton, Fitzgerald, & Cooper, 1999), epilepsy (Goldberg-Stern et al., 2001) or acute leukaemia (Ross, Spector, Robison, & Olshan, 2005). There is great variability as to the associated physical features in Trisomie 21. Among the distinct facial characteristics are the upward slanting eyes, a rounded fold of skin at the inner corner of the eye (epicanthal fold), a flattened nose, or a protruding tongue. The hands are often small with short, broad fingers, and they may show a single crease (simian crease) in the palm. The muscle tonus in the infant is reduced, which may affect feeding and crying behaviour and contribute to faster weariness.

Motor, language and cognitive development are delayed. The degree of mental retardation can vary tremendously. Most frequently, however, a slight to moderate retardation is present (Nicham et al., 2003). The risk of behavioural disturbances in Down's Syndrome children is increased, although not as much as in other intellectual disabilities (Stores, Stores, Fellows, & Buckley, 1998). According to parental reports about a third of the children with Down's syndrome display maladaptive behaviour (Gath & Gumley, 1987). There appears to be an age-related shift from externalising behaviour to more internalising behaviour with advancing age. More specifically, children typically show more opposition, stubbornness or inattention, whereas adolescents and young adults with Trisomy 21 are more likely to experience anxiety and depressive mood, or to display withdrawal behaviour (Dykens, Hodapp, & Evans, 1994).

Table 2.2: Congenital heart defects in genetic syndromes; [1](Scambler, 2000), [2](Laufer-Cahana, 2002), [3](Basson & Vaughan, 2004).

Syndrome	Prevalence	CHD frequency	CHD type	Characteristics
Noonan Syndrome	1/1,000 to 2,500	50-90%	PS ASD VSD TF partial AVSD	short stature, broad neck, chest deformity, facial appearance, maldescended testis; risk of coagulation defects and lymphatic dysplasias; developmental delay; mild mental retardation in 1/3
22q11 deletion[1]	1/4,000	75%	interrupted aortic arch patent truncus arteriosus TF	facial dysmorphism; hypoplastic thymus gland; learning difficulty, behavioural problems, increased risk of psychotic illness
Turner Syndrome	1/2,500- 3,000 females	17-45%	CoA aortic valve anomalies HLHS	short stature, wide neck; absence of 2nd sex chromosome, gonadal dysgenesis; defect lymphatic system (oedema); specific learning deficits, mental retardation in 10%
Trisomy 18 (Edwards S.)	1/6,000	90%	polyvalvular disease VSD DORV AVSD TF	high infant mortality; craniofacial appearance, distinctive hand posture, overriding fingers; severe psychomotor and growth deficiencies
VACTERL Association	1.6/10,000	80%	any type	on average 3-4 of the following features: V - vertebral defects A - anal atresia C - cardiac anomalies T - tracheoesophagal fistula E - oesophageal atresia R - renal defects L - limb (radial) very complex clinical management; growth difficulties; developmental delay; behavioural difficulties
Williams Syndrome	1/10,000	80%	narrowing of aorta AS PS	dysmorphic facial features, short stature; connective tissue abnormality; developmental delay, unique cognitive profile, personality (empathy, overfriendliness), attention deficit
CHARGE association	1/10,000-12,000	60-85%	TF DORV truncus arteriosus AVSD	C - coloboma H - heart defects A - atresia of airways R - retardardation of growth and/or development G - genital defects E - ear anomalies and/or deafness additional abnormalities; learning difficulties in 60-100%
Trisomy 13	1/10,000 - 20,000	80%	polyvalvular disease ASD VSD DORV	orofacial cleft, microphthalmia, polydactyly of the limbs; growth deficiency; psychomotor retardation
Wolf-Hirschhorn Syndrome	1/50,000	50%	ASD PS VSD PDA TF	broad prominent nasal bridge; growth deficiencies; multiple congenital anomalies; neurological deficits, mental retardation
Ellis-van Crefeld Syndrome[2]	1/60,000	50-60%	common atrium ASD VSD	short stature, short extremities, dwarfism, narrow chest, polydactyly
Holt-Oram Syndrome[3]	1/100,000	<75%	ASD VDS	upper limb deformity; carpal bone abnormalities (sometimes fusion)

A wide range of other genetic syndromes presents with CHD. Table 2.4 gives an overview of selected syndromes summarising their prevalence, the relative frequency of CHD, the most frequent type of CHD, and their cardinal features. The information presented was extracted from the book edited by Cassidy and Allanson unless stated otherwise (Cassidy & Allanson, 2005).

In sum, genetic syndromes in a child, which often involve malformation of the heart, impose many challenges on affected families in their everyday lives. Depending on which syndrome is present, their child may differ from other children in physique, demands for medical care, growth, motor and cognitive development, language abilities and/or behavioural characteristics. Genetic defects, as well as heart defects as part of a syndrome or by themselves, are associated with various implications in everyday life both for the child and the family. They will be considered in the following chapter.

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3 Living with congenital heart disease

Some four decades ago Glaser and colleagues provided insights into the everyday life experiences, fears and perceptions of mothers of children with CHD (Glaser, Harrison, & Lynn, 1964). Although the personal approach to illness and child-rearing practices may have changed since then, the comments clearly illustrate the potential implications of CHD both for the parents and for the child affected:

We didn't understand him because, constantly, he had to sit on someone's lap. He had a terrible disposition and we would get so tired out. (p. 371)

If he hadn't been sick as much as he was, I would have clamped down on him a little more, and he wouldn't be quite as spoiled as he is. (p. 373)

I just close my eyes and give him two good swats and tell him to hush, and I know if I don't punish him I am going to have a spoilt brat on my hands. (p. 374)

I guess it's just because he has always been little and puny and weak, and always getting hurt and something happening to him that I just can't help but watch him. (p.371 f.)

It was such a strain on us that I think we were a little rougher with him than we needed to be. (p.371)

Various questions arise when reading these comments. For instance, do children with CHD differ in their behaviour from other children? What may cause behavioural difficulties in children with an inborn heart defect? Other question may concern parental well being: How do parents cope with the illness of their child? Are there risk factors or factors of resiliency, which determine the psychological adjustment in these parents? In the following section, current empirical findings addressing some of these aspects are discussed.

3.1 Implications for the child

Chronic disease in childhood increases the risk of suffering from increased levels of psychosocial distress in the affected children (Barlow & Ellard, 2006). Based on a meta-analysis Lavigne and Faier-Routman estimated that twice as many children with chronic disease suffer from psychological maladjustment as do otherwise healthy children (Lavigne & Faier-Routman, 1992). Internalising and externalising behavioural difficulties as well as a poor self-esteem have frequently been observed in chronic paediatric illness. The disease itself may impose physical disability or physical constraints on the children, which distinguishes them from their healthy peers. Furthermore, they may be confronted with the worries of their parents reflecting altered child-parent interactions (Maccoby, 1992). Indeed the interaction between children with CHD and their parents, for instance during feeding or interactive play, has been reported to differ in terms of responsiveness in mothers and signalling cues by the children (Lobo, 1992), or in terms of levels of engagement and affect in children with CHD and their mothers (Gardner, Freeman, Black, & Angelini, 1996). Considering these diverse aspects it is of general interest, whether the overall quality of life in children with chronic or inborn disease is affected, too. With regard to CHD, it is of interest whether living with a malformation of the heart influences the way children perceive their quality of life. Before empirical findings regarding the quality of life in CHD are considered, the definition and measurement of the construct will be outlined.

3.1.1 The concept and measurement of quality of life

Quality of life (QoL) is a hypothetical construct that combines numerous facets of life, for instance physical and mental health, standard of living, familial circumstances, social integration, and spiritual contentment. Thus, on one hand QoL is characterised by objective characteristics such as income, employment, presence or absence of physical disability. On the other hand, QoL depends on an individual's perception and subjective evaluation of those characteristics and their subjective evaluation. Many attempts have been made to specify core concepts and core dimensions (Felce & Perry, 1995; Jenney, 1998). General agreement, however, exists only on the multidimensionality of the construct. Koot, for instance, objected to the idea of a generally valid definition of QoL (Koot, 2001). Instead, he proposed to view QoL as a working construct, which is restricted to the specific domains of research interest. Within the current context of CHD this implies focussing on the health-related dimensions of QoL. These consist of the somatic, the behavioural, the emotional, the cognitive, and the psychosocial domain. The concept of health-related QoL has nowadays widely been excepted as an endpoint in medicine and clinical trials have begun to incorporate QoL instruments (Bullinger, 2002).

The measurement of QoL is as diverse as its conceptual approach. Various instruments have been developed. They include generic as well as disease-specific tools. The former can be applied to any and across populations independent of their health status, e.g. the SF-36 (Bullinger & Kirchberger, 1998). The latter tools enquire about the impact of physical symptoms, medical surveillances, and worries relating to the disease, e.g. the CHD-TAAQOL (Kamphuis et al., 2004). Combinations of generic and disease-specific instruments also exist. A further differentiation is based on the use of self- or proxy-reports. While it is likely that the best informant on QoL is the individual of concern herself, it is not always possible to receive the information by means of self-reports. In case of young age, the inability to comprehend the enquiry, or in case of severe illness, someone close to the patient may also serve as a source of information.

In sum, QoL is a highly subjective, multidimensional and hypothetical construct. Among the main dimensions that matter for a health-related context are those, which touch upon somatic, behavioural, emotional, cognitive, and psychosocial issues. Numerous instruments for the QoL assessment exist by means of self- and proxy-report measures.

3.1.2 Quality of life in children with CHD

In CHD neurodevelopmental difficulties, cognitive problems and aberrant behaviour have been observed in a proportion of children (see sections 2.3.2; 2.4; 3.1.). Thus, as physical, neurodevelopmental, and behavioural aspects contribute to the overall QoL in the individual, it may be inferred that children with CHD experience an impaired QoL compared to healthy children. Krol and colleagues investigated the QoL in children and adolescents with minor to very complex CHD as perceived by themselves or by their parents (Krol et al., 2003). They observed that children with CHD and their parents perceived motor functioning and autonomy to be reduced compared to healthy children. The parents also reported on lower cognitive functioning in their child. Hence, difficulties with motor activities such as running, or climbing stairs, as well as activities which require independence such as going to school or washing oneself were reported to have a considerable impact on the QoL in CHD. In contrast, the physical, the social and the emotional dimensions compared to those in healthy children across self- and proxy-reports. Interestingly, the severity of the heart defect did not relate to any of the QoL dimensions.

Moyen Laane and colleagues observed a good overall QoL in children with spontaneously cured CHD, children treated with cardiac surgery, and children with CHD with genetic syndromes (Moyen Laane et al., 1997). Analyses of the external, interpersonal, and personal psychological subdimensions demonstrated positive and negative aspects perceived by these children. For instance, children who had undergone surgical repair as well as children with genetic syndromes reported dissatisfaction with peer acceptance. In addition, the latter group experienced a reduced self-esteem. On the positive side, satisfaction with social support was better compared to healthy controls and there were fewer psychosomatic problems in CHD.

The result of both studies demonstrate that there may be some aspects relating to QoL, which are affected in CHD but also dimensions which do not differ from the general population. However, the findings can not easily be generalised to children with CHD who have undergone open-heart surgery under the heart-lung machine. This mode of surgical intervention is associated with a wide range of short-term and long-term side effects and risks for the immune system, for neurodevelopment, and for the central nervous system (see section 2.3.2). Also, from a psychological point of view the event of open-heart surgery may have long-lasting effects on the child as the memories of hospitalisation may not easily be forgotten. What is more, the improvement of surgical technique enables surgical correction of heart defects that, only a few years ago, run a fatal course. These children have now reached adolescence or young adulthood and little is known about their QoL. Thus, there is a great need for the systematic evaluation of recent studies, which have addressed QoL and psychological adjustment in children with CHD who have undergone open-heart surgery under use of the heart-lung machine.

3.2 Implications for the parent

The comments by mothers of children with CHD (Glaser et al., 1964) cited in the introduction of this chapter do not only illustrate that some children with CHD may display difficult behaviour, they also demonstrate the distress some parents may suffer. Further, some mothers described a parenting stile characterised by overprotection but also by physical abuse. Either may be the result of insufficient coping processes or maladjustment to the illness of their child. To date, few studies have evaluated the psychological adjustment, the well-being and the QoL in parents of children with CHD. They will be discussed in the following section.

3.2.1 Quality of life in parents of children with CHD

Parents of children with CHD are generally at a higher risk for experiencing parenting distress (Uzark & Jones, 2003), psychological distress (Goldberg, Morris, Simmons, Fowler, & Levison, 1990; Emery, 1989) and hopelessness (Lawoko & Soares, 2002). Heightened levels of anxiety and depression, as well as concerns relating to the illness of their child have been reported particularly for mothers (van Horn, DeMaso, Gonzalez-Heydrich, &

Erickson, 2001; Rona, Smeeton, Beech, Barnett, & Sharland, 1998). Family relationships and family life may be affected in different ways (Wray & Maynard, 2005; Hauser et al., 1996). Although most studies have demonstrated increased mean values for indices of distress and discomfort in groups of parents of children with CHD, the studies also observed a great variability as to parents' psychological adjustment. This highlights the need for understanding what predisposes parents to maladaptive responses and which factors increase resilience.

With regard to QoL, Lawoko and Soares compared self-reports of mothers and fathers of children with CHD with self-reports of parents of children with other chronic disease or with healthy children. The overall QoL was reduced in parents of children with CHD compared to the parents of children with healthy children (Lawoko & Soares, 2003). Analysis of sub-scales revealed that the physical and the psychological dimension determined the observed group differences. Mothers of CHD children appeared most affected as they reported on even lower levels of QoL than CHD fathers. Interestingly, the authors investigated determinants of QoL across all parents and noted that child-specific factors including the child's health explained only one percent of the variance in QoL. More variation was explained by parent-specific variables such as marital status and education (8%), employment (11%), and financial strain (15%). Most importantly, levels of psychological distress and hopelessness accounted for more than 25% of the overall variation in QoL. From there it appears that the mere instance of rearing a child with CHD does not consequently lead to psychological distress or a reduction in QoL. More important determinants may relate to personal and environmental characteristics. However, research into what determines psychological maladjustment or a reduced QoL in parents with CHD children is scarce and needs further elaboration.

3.2.2 Open-heart surgery from the parental perspective

Besides issues relating to the everyday life difficulties that may be imposed on families with a child with CHD, actual heart surgery in the child is a more temporary event. Heart defects that acutely threaten life or defects associated with long-term cardiac complications must be surgically corrected or at least palliated.

Parental distress and coping before cardiac surgery

Clearly, facing surgery of the heart is an extremely distressing event for the affected children and their parents. Uncertainties about the surgical outcome, fears of risks and postoperative complications may contribute to heightened anxiety during the time before surgery. On the other hand, optimism and hopes for an improved QoL for the period to follow may be felt. Utens and colleagues studied psychological distress and acute coping behaviour in parents five weeks before elective cardiac surgery in their child with CHD (Utens et al., 2000). Mothers experienced heightened overall psychological distress, particularly increased anxiety, sleeplessness and social dysfunctioning. Fathers reported on impaired social functioning. Parental coping was characterised by a reduced expression of annoyance or anger. Further, mothers displayed less problem solving activities and passive reaction patterns such as socially isolating themselves, inertia or worrying compared to a reference group. Another study also demonstrated higher rates of psychological distress in 63% of mothers and 48% of fathers before cardiac surgery in their child compared to a group of healthy parents (Wray & Sensky, 2004). Levels of distress were comparable to a group of parents who awaited bone marrow transplantation in their child with a malignant disease. Considering the effect of the severity of the heart effect on parental stress, there were no differences in rates of psychological distress between parents of children with cyanotic and acyanotic defects.

In sum, elevated levels of psychological distress, particularly in mothers, were observed in parents before cardiac surgery of their child. Inadequate coping stiles may be employed by some affected parents. Consequently it is of interest whether symptoms of anxiety and distress resolve in parents once the surgical intervention has been completed.

Acute postsurgical distress and long-term adjustment in parents

Open-heart surgery requires the stay on an intensive care unit for the child immediately after surgery until stability of the circulatory system is ensured. To our knowledge, levels of acute psychological distress in parents of children after heart surgery in relation to the experience of intensive medical care have not been assessed. Nevertheless, some work has been conducted focussing on parents of children generally admitted to a paediatric intensive care unit. Thus, mothers of children hospitalised on a paediatric intensive care unit were observed to experience greater levels of state anxiety, depression, confusion, anger and stress compared to mother of children hospitalised to general paediatric ward (Berenbaum & Hatcher, 1992; Board & Ryan-Wenger, 2003). Haines and colleagues highlighted the distressing aspect of the unfamiliar nature of the highly technological environment of an intensive care unit, in particular the frightening array of technological equipment associated with intubation. Parents reported that the painful procedures subjected to their child, the sight and sounds on the ward, and their child's reaction to intensive care were causing the most distress (Haines, Perger, & Nagy, 1995). Miles and colleagues observed that the child's behaviour and emotions were the main determinants of parental distress as opposed to environmental sights, sounds or procedures. Moreover,

Table 3.1: Diagnostic criteria for traumatic stress disorders

Diagnostic criteria
Acute Stress Disorder (ASD)
A. Individual experience (or witnessing) of a traumatic event including a subjective response of fear, helplessness, or horror
B. At least three symptoms of dissociation, e.g. depersonalisation, dissociative amnesia
C. Marked symptoms of re-experience, avoidance, and hyperarousal
D. Symptoms lasting from 2 days to one month
E. Symptoms impairing individual everyday life functioning
Posttraumatic Stress Disorder (PTSD)
A. Individual experience (or witnessing) of a traumatic event including a subjective response of fear, helplessness, or horror
B. At least one re-experiencing symptom (e.g. intrusive thoughts)
C. At least three avoidance symptoms (e.g. avoidance of trauma-related stimul)
D. At least two hyperarousal symptoms (e.g. difficulties with concentration)
E. Symptoms lasting for at least one month
F. Symptoms impairing individual everyday life functioning

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, APA, 1994

parents perceived the alteration in their role as particularly distressing. Parental role alterations involved the inability to protect the child and not knowing of how to best help the child (Miles, Carter, Riddle, Hennessey, & Eberly, 1989).

From a clinical point of view the focus should not only be restricted to levels of acute distress during the child's hospitalisation, but also to the question whether the experience of intensive care potentially causes levels of clinically relevant acute and posttraumatic stress in affected parents. Table 3.1 provides the diagnostic criteria for Acute Stress Disorder (ASD) and for Posttraumatic Stress Disorder (PTSD) according to the DSM-VI (APA, 1994).

A recent prospective cohort study measured the prevalence of ASD in 272 parents of infants and children more than 48 hours after admittance to a paediatric intensive care unit and the prevalence of PTSD two months after discharge from intensive care (Balluffi et al., 2004). One third of the sample met diagnostic criteria for ASD. The severity of ASD symptoms was associated with an unexpected admission and parental worries regarding the child's death. Neither objective severity of the child's illness nor the parental perception of illness severity related to the presence of ASD. The two months-follow up revealed that 21% of the parents still experienced significant traumatic stress as they met the diagnostic criteria of PTSD. Analyses of risk factors for PTSD in these parents demonstrated that the presence of ASD during hospitalisation of the child and the severity of ASD symptoms predicted the development of PTSD in parents.

Considering the context of this thesis, the previous study results highlight the potentially traumatising character of intensive care-related experiences for parents. Thus, even after successful open-heart surgery parents of children may be at increased risk to suffer from posttraumatic stress and psychological maladjustment. It is yet to determine to what extent findings regarding the general population of parents of children in need for intensive care apply to parents of children with CHD undergoing open-heart surgery. Moreover, risk factors need to be identified indicating who may be particularly vulnerable.

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4 Psychological adjustment and quality of life in children and young adults after open-heart surgery for congenital heart disease - A systematic review

4.1 Abstract

Context: Medical advances in surgical techniques and bypass procedures have reduced mortality in congenital malformations of the heart. Therefore, quality of life (QoL) and the emotional impact of surviving open-heart surgery are of major interest.
Objectives: To summarise the evidence on psychological adjustment and health-related QoL in children and young adults, who underwent open-heart surgery for congenital heart disease (CHD). Further, to identify reported associations between medical, individual or environmental factors and psychological adjustment or QoL.
Data sources: We searched EMBASE, MEDLINE, CINAHL, PsycINFO and international databases for dissertations using multiple search terms. Search terms related to CHD, open-heart surgery, cardiopulmonary bypass, psychological adjustment, and QoL. Reference lists of relevant studies and reviews were explored. Corresponding authors were asked about unpublished data.
Study selection and data extraction: Studies evaluating psychological adjustment or QoL after early open-heart surgery for CHD, published between 1990 and 2005, with a mean postoperative follow up of at least two years were included. Studies published in English, German, French and Italian were eligible. Two reviewers, blinded to the origin of the reports, rated the methodological quality of the studies according to a standardised checklist. Inter-rater reliability was high (Cohen's kappa = 0.85). Results of self-reports or proxy-reports on psychological adjustment and QoL were extracted. Heterogeneity of study populations and methodological approach did not permit formal meta-analysis.
Data synthesis: Twenty-five studies were included with a total of 2,100 children or young adults. Despite inconsistencies in findings a number of trends were identified: (a) prevalences of psychiatric disorders were increased in cyanotic CHD; (b) most parents reported psychological difficulties in their child after surgery, except for children with transposition of the great arteries; (c) self-reports by children with CHD indicated good

psychological adjustment. Among the identified risk factors for psychological maladjustment were deep hypothermic circulatory arrest, physical and intellectual impairment, and parental distress. Only few studies evaluated the overall QoL in operated CHD. With reservation, current data suggest: (d) a good QoL in children with operated CHD; (e) an impaired QoL in young adult survivors. Defect severity, physical capacity, and duration of cardiopulmonary bypass time related to QoL after open-heart surgery.
Conclusion: Future research will need to address the current methodological weaknesses that, to date, impede conclusions as to the direct effect of open-heart surgery in CHD on psychological adjustment and QoL. Assessing the prospective course of psychological outcome and QoL while controlling for the effect of chronic illness will help us to understand the needs of operated CHD survivors in the long-term.

4.2 Introduction

CHD occurs in 4-12 per 1,000 live births (Pradat, Francannet, Harris, & Robert, 2003; Botto, Correa, & Erickson, 2001; Meberg, Otterstad, Froland, Lindberg, & Sorland, 2000; Schoetzau, Santen, Sauer, & Irl, 1997). Severity of CHD ranges from small septal defects, which close spontaneously, to complex malformations of the heart that potentially cause an early death. About a third of the children with CHD is born critically ill necessitating cardiac surgery within the first year of life (Samanek, 2000; Ferencz et al., 1985), while other children require surgical correction in childhood or later in life to prevent late cardiac complications. As medical advances in surgical, anaesthetic, and postoperative supportive care techniques have significantly reduced mortality in CHD, the population of CHD survivors has considerably increased (Allen, Gauvreau, Bloom, & Jenkins, 2003; Boneva et al., 2001; Stark et al., 2000). In particular, surgical correction of more severe cardiac malformations has experienced dramatic improvements during recent years (Eskedal et al., 2005; Meberg et al., 2000). Currently, surgical interventions produce acceptable mid-term and long-term survival rates even in high-risk infants, such as premature and low-birth-weight children (Bove et al., 2004; Oppido et al., 2004). Nevertheless, risk factors relating to issues of morbidity and mortality remain. In particular, the application of extracorporeal circuitry during open-heart surgery can cause inflammatory responses, myocardial injury, damage to the kidneys and neurological injury (Murphy & Angelini, 2004). With regard to the long-term outcome, neurodevelopmental delay and cognitive impairment have been associated with the event of open-heart surgery in some children (Bellinger, Bernstein, Kirkwood, Rappaport, & Newburger, 2003; Limperopoulos et al., 2002; Wernovsky et al., 2000).

Hence, as open-heart surgery offers the chance to correct or palliate CHD, it also sets the challenge of psychologically adjusting to the surgical event and its associated side effects. The impact of the surgery extends beyond physical outcome as it determines many aspects of QoL in these patient. During the last decade clinical research has increasingly adapted to the somatic understanding of illness by considering psychological factors or the QoL in patients.

To understand the existing findings in the CHD literature the relevant terminology is briefly introduced: *Psychological adjustment* incorporates a wide range of outcome measures including behavioural and psychosocial issues or aspects of personality such as self-esteem. One of the most common approaches considers the presence of behavioural difficulties by differentiating between *internalising* and *externalising behaviour* (Achenbach & Edelbrock, 1983). The former is characterised by symptoms of anxiety, depressive mood, withdrawal behaviour or somatic complaints, while the latter considers delinquent, aggressive, and show-off behaviour. The concept of QoL expands on the psychological dimension. QoL is generally understood as a multidimensional construct integrating an individual's perceptions with respect to the domains of physical health, psychological well being, social integration, emotional and cognitive functioning (Koot, 2001). In the context of patient populations it is referred to as health-related QoL. Generic as well as disease-specific instruments exist. The former are used with any patient population independent of their specific disease, while the latter assess disease-specific issues. Also, there are some QoL instruments that combine generic with disease-specific items. Psychological adjustment as well as health-related QoL can be assessed by means of self-reports or proxy-reports.

In the face of the growing literature on psychological adjustment and QoL after open-heart surgery, this review aims at the systematic assessment of studies on affected children, adolescents and young adults, specifically after surgery with cardiopulmonary bypass. In addition, data suggesting possible associations between long-term outcome and medical, individual and environmental risk factors are summarised.

4.3 Data sources

4.3.1 Search strategy

For the period between 1990 and June 2005 an electronic literature search was conducted via EMBASE, MEDLINE, CINAHL, and PsychLIT to identify potentially eligible studies and review articles. We chose this time period in order to reduce the variance in observed outcomes due to time-dependent advances in surgical and support techniques. Additionally, international databases of dissertations and theses were searched for the same time period (ProQest, NDLTD). An initial search used the EMBASE identifiers *congenital heart disease, congenital heart defects, open-heart surgery; cardiac surgery, cardiopulmonary bypass, circulatory arrest, switch operation, Mustard, Senning, Rastelli, quality of life, psychological, psychiatric, psychopathology, mental health, subjective health, behavio*r, development, adjustment, and adaptation.* The Boolean operator "and" was used to combine identifiers for patient population, intervention, and outcome. The Boolean operator "or" was used to combine identifiers within those three search areas. Publications in English, German, French and Italian were considered for inclusion. Thus, 595 hits were generated. Titles and abstracts were screened for eligibility. Full texts of pre-selected articles were thoroughly checked for inclusion and exclusion criteria according to a predefined standardised checklist by two independent reviewers (details and forms are provided in Appendix A). In addition, reference lists of the relevant studies and reviews were examined to identify other pertinent articles. Corresponding authors of relevant reports and investigators from the field were contacted and asked whether they would be able to provide any unpublished data.

4.3.2 Study selection

Studies were included if they met the following criteria: *Types of studies:* Case control or cross-sectional studies, prospective or retrospective cohort studies. *Types of participants:* Children, adolescents and young adults up to a mean age of 25 years with congenital malformation of the heart or the great vessels as defined by clinical diagnosis. *Types of surgical intervention:* Open-heart surgery with cardiopulmonary bypass including corrective surgery with or without the need for later re-operation, staged or palliative surgical procedures. Studies were included if more than 50% of the sample had undergone open-heart surgery. Studies primarily including patients with heart or heart-lung transplantation were not eligible. *Types of outcome measures:* Quantitative self-reports, proxy- or examiner's reports of QoL, and measures of psychological adjustment with a mean postoperative follow up of at least two years. Outcome measures assessed by means of questionnaires or structured interviews were included.

In the case of missing information, the corresponding authors were contacted. Reasons for exclusion were recorded (see Appendix A). Accordingly, twenty-five published studies met the inclusion criteria. One dissertation was considered pertinent to the review question (Visconti, 2000). As the main results of the dissertation were available in the form of a published article, results were extracted from its paper version. We did not identify any unpublished data eligible for inclusion.

4.3.3 Quality assessment of methodology

Methodological quality of the included studies was rated independently by two reviewers. To minimise bias the reviewers were blinded to title, author, institution and bibliography of the article. A standardised checklist was developed for the purpose of this review using criteria related to recruitment, study design, operationalisation of outcome, and statistical analyses (see Appendix A). Inter-rater reliability for the rating scores was assessed by means of Cohen's kappa, which amounted to 0.85. In the case of disagreement, consensus was achieved by discussion between the two reviewers. If agreement was not achieved, a third reviewer decided on the scores.

4.4 Data synthesis

4.4.1 Description of studies

Origin: Most published data were from single centre studies in Europe (12) and North America (10). Three studies originated from Australia. The majority of studies included focused on psychological outcome (n=21). QoL was assessed in five studies (Mussatto & Tweddell, 2005; Ekman-Joelsson, Berntsson, & Sunnegardh, 2004; Hoevels-Guerich et al., 2002; Kamphuis et al., 2002; Walker, Temple, Gnanapragasam, Goddard, & Brown, 2002).

Design: We distinguished between those studies specifically addressing outcome after open-heart surgery (n=18) and studies evaluating outcome in children with CHD in general where more than half of the cases had undergone open-heart surgery (Ekman-Joelsson et al., 2004; Salzer-Muhar et al., 2002; Saliba et al., 2001; Gupta, Giuffre, Crawford, & Waters, 1998; Bjornstad, Spurkland, & Lindberg, 1995; DeMaso, Beardslee, Silbert, & Fyler, 1990). Only one study prospectively followed up psychological adjustment (Visconti, Saudino, Rappaport, Newburger, & Bellinger, 2002). The majority of studies compared their results to published norms. Five studies included a healthy control group (Karl et al., 2004; Salzer-Muhar et al., 2002; Saliba et al., 2001; Kern, Hinton, Nereo, Hayes, & Gersony, 1998; Oates, Turnbull, Simpson, & Cartmill, 1994). Four studies had a control group characterised by minor heart defects (Walker et al., 2002; Goldberg et al., 2000; Wright & Nolan, 1994; DeMaso et al., 1990) and another two studies used a control group with non-cardiac illness (Mussatto & Tweddell, 2005; Dunbar-Masterson et al., 2001).

Sample characteristics: Sample size varied between 14 and 306 cases. Some studies repeatedly assessed the same cohort of patients publishing several reports. Thus, the total number of patients followed up in the studies included amounts to approximately

2,100. The overall male to female ratio showed a predominance of males (3:2). Most studies excluded children with significant non-cardiac anomalies and intellectual impairment. About half of the studies assessed a homogeneous diagnostic sample consisting of transposition of the great arteries (TGA), hypoplastic left-heart syndrome (HLHS) or pulmonary atresia (PA). The other half included heterogeneous samples covering a wide range of defects. Accordingly, a wide range of operative techniques had been performed. Age at the first open-heart surgery ranged from a few days to just under 15 years. Most studies included a population of children who had undergone surgical intervention during infancy. The studies had a postoperative follow-up interval ranging from two years to 20 years. Mean ages at follow up ranged from 2.6 years to 24.3 years. Most studies assessed psychological adjustment or QoL during school age. Risk assessment: Potential risk factors for the postoperative outcome were assessed by a majority of the studies. They can be categorised into factors relating to the heart defect itself (e.g. diagnosis, cardiac status, presence of cyanosis), to pre-, peri- and postoperative surgery variables (e.g. deep hypothermia with circulatory arrest, duration of circulatory arrest), to child-specific factors (e.g. IQ, language), and to environmental aspects (e.g. parental distress). Medical data and cognitive development were the aspects most frequently considered.

An overview of characteristics and main results of the studies included is given in table 4.1.

4.4.2 Methodological quality

Overall: Methodological quality varied greatly across studies. Individual quality ratings are listed in table 4.1. Scores for seven of the 25 studies were in the upper third of the quality rating (scores from 9-12) and considered to be of high impact regarding the research question. The remaining studies scored in the medium range (scores from 5-8). *Sample recruitment:* Inspection of recruitment strategies showed that 52% of the studies achieved the maximum score or one score below. *Design:* None of the studies under review received the maximum score. Only one study prospectively assessed the course of psychological adjustment (Visconti et al., 2002). Most studies evaluated the outcome using single informants. *Outcome assessment:* Operationalisation of outcome was heterogeneous across reports. All but three studies used standardised, validated and psychometrically evaluated measures. An overview of the standardised instruments in use is given in table 4.2. *Statistical data analyses:* Maximal rating scores were obtained by seven of the 25 studies. This implied that authors had considered the statistical test assumptions (e.g. deviation from normal distribution) and had adjusted for potentially confounding variables (e.g. by means of regression analyses).

Table 4.1: Summary table of included studies assessing psychological adjustment and/or QoL in children, adolescents and young adults after open-heart surgery in young age

	study origin	N (% male) response	CHD	exclusion criteria	surgical age follow up age	follow up interval	controls	assessed risk factors	outcome	results	rating (0-12)
1	Alden 1998 Sweden	31 (68) 100%	TGA	rapid health deterioration	mean: 1.6 yrs/ mean: 13.2 yrs	11.5 yrs	norms	cardiac status; IQ	DSM-IV diagnosis self-esteem	*clinical diagnosis:* · 19% met criteria for DSM-IV diagnoses (separation anxiety, social phobia, dysthymia, oppositional defiant disorder) *self-report* ↔ · self-esteem comparable to norms *associations:* · more behavioural difficulties in children with need for re-operation · no association between IQ and behaviour or self esteem	10
2	Bellinger 1997 USA, Boston[1]	113 (>) 68%	d-TGA	congenital and extracardiac anomalies; birth weight < 2500 g	mean: < 3 months/ mean: 2.6 yrs	2 yrs	norms	DHCA vs. CBP; expressive language	behaviour	*proxy report* ↑ · fewer behavioural problems *associations* · disadvantage for DHCA for overall and internalising behaviour · more behavioural difficulties with expressive language delay	9
3	Bjornstad 1995 Norway	26 (62) 87%	severe cyanotic CHD	blindness; chromosomal anomalies	not reported/ mean: 16.3 yrs	> 2 yrs *	none	physical capacity	DSM-IV diagnosis behaviour, psychosocial functioning	*clinical diagnosis:* · 46% met criteria for at least one DSM-IV diagnosis mostly anxiety and depressive spectrum disorders, also attention deficit and conduct disorder *proxy report* ↓ · 19% with significant behavioural difficulties · 35% with poor psychosocial functioning · 50% with moderate to severe family difficulties *associations:* · physical capacity related to psychological and psychosocial functioning	8
4	Culbert 2003 Canada	306 (71) 51%	TGA	intellectual impairment	<15 days/ mean: 13 yrs	13 yrs	norms	heart defect; repair technique	well being	*self-report* ↑ · physical and mental health better than norms · self-esteem comparable to norms *associations:* · TGA/VSD/PS with lower physical and mental health than TGA and TGA/VSD children · ASO patients with better self-esteem, physical and mental health compared to other surgery groups · several perfusion parameters related to social limits and behaviour concepts	7

Table 4.1: continued

	study origin	N (% male) response	CHD	exclusion criteria	surgical age follow up age	follow up interval	controls	assessed risk factors	outcome	results	rating (0-12)
17	Saliba 2001 France	67 (47) 80%	single ventricle anatomy	learning difficulties	not reported/ 22.7 yrs	> 2 yrs *	healthy controls	cyanosis; SES; age	mental health	*self-report* ↔ · mental, social and general health, self-esteem, and dysfuncioning measures within norms *associations:* · cyanosis and educational level inversely related to physical and general health perception	8
18	Salzer-Muhar 2002 Austria	48 (69) 79%	d-TGA TF other	chromosomal and extracardiac anomalies	not reported/ mean: 13.7 yrs	> 2 yrs *	healthy controls		behaviour, self-concept; personality; anxiety	*self-report* ↔ · behaviour within norms · lower state anxiety, higher superego strengths · CHD male adolescents perceive reduced self-esteem and physical capacity	6
19	Utens 1993 Netherlds[2]	CBCL: 144 (59) 87% YSR: 179 (59) 86.5%	VSD TGA TF PS other	Trisomy 21	< 15 yrs/ CBCL: 10-12 yrs YSR: 11-17 yrs	9 yrs plus	norms	heart defect; IQ	behaviour behaviour	*proxy report* ↓ · more behavioural difficulties *self-report* ↓ · more behavioural difficulties *associations:* · no association between heart defect and behaviour · negative correlation between proxy-reported behaviour and IQ, no correlation with self-perceived behaviour	8
20	Utens 1994 Netherlds[2]	288 (51) 86%	ASD VSD TGA TF PS other	Trisomy 21	< 15 yrs/ mean: 22.7 yrs	16 yrs	norms	heart defect	hostility, self-esteem, neuroticism, social functioning	*self-report* ↔ · lower hostility and neuroticism, higher self-esteem · good social functioning · more patients with disability pension, less patients live by themselves *associations:* · no effect for type of heart defect	6
21	Utens 1998(a) Netherlds[2]	166 (not reported) 81%	ASD VSD TGA TF PS other	Trisomy 21	< 15 yrs/ mean: 21.7 yrs	> 9 yrs	norms	heart defect; IQ	behaviour	*self-report* ↓ · more overall behavioural difficulties · more somatic complaints and strange behaviour *associations:* · no effect of type of heart defect or IQ on behavioural adjustment	8

Table 4.1: continued

	study origin	N (% male) response	CHD	exclusion criteria	surgical age follow up age	follow up interval	controls	assessed risk factors	outcome	results	rating (0-12)
5	DeMaso 1990 USA, Boston	140 (>) not reported	TGA TF	not reported	not reported/ mean: 5.7 yrs	> 2 yrs *	spontaneous recovery	heart defect; CNS impairment; IQ; sex	emotional adjustment	*proxy report* ↓ · poorer emotional functioning *associations* · strong association between reduced emotional functioning and CNS/ IQ impairment · no effects for heart defect or sex	8
6	Dunbar- Masterson 2001 USA, Boston[1]	155 (76) 96%	d-TGA	congenital and extracardiac anomalies; birth weight < 2500 g	median: 6 days/ median: 8.1 yrs	8 yrs	norms; asthma, JRA, ADHD	peri-, post- operative data; IQ SES	well being	*proxy report* ↔ · psychosocial and physical health within norms · more difficulties on single aspects, i.e. attention, learning, and speech · psychosocial health worse compared with asthma and JRA, *associations:* · psychosocial scores associated with intellectual ability and with comorbidities · no effects for heart defect, treatment, CA time, no. of surgeries, operative age, or SES	10
7	Ekman- Joelsson 2004 Sweden	42 (45) 81%	PA	no exclusion	not reported/ median: 8.5 yrs	> 2 yrs *	norms		QoL	*proxy/ self-report* ↔ · overall QoL, self-esteem and peer acceptance within norms · lower satisfaction with activities, more psychosomatic complaints · parental working and housing conditions within norms · higher level of income and satisfaction with financial situation · more parent-child interaction, yet reduced satisfaction with familial and social life	8
8	Goldberg 2000 USA, Michigan	61 (66) 58%	HLHS	not reported	< 2 months/ mean: 4.8 yrs	> 2 yrs *	non-HLHS- FSV mal- formation		behaviour	*proxy report* ↔ · internal, external and overall behaviour within norms · adequate communication, socialisation and daily living skills *associations:* · no differences between diagnostic groups	5

Table 4.1: continued

	study origin	N (% male) response	CHD	exclusion criteria	surgical age follow up age	follow up interval	controls	assessed risk factors	outcome	results	rating (0-12)
9	Gupta 1998 Canada	39 (38) 98%	cyanotic/ acyanot. CHD	not reported	not reported/ mean: 10.1 yrs	not reported	norms	cyanosis; parental anxiety	behaviour fear, anxiety, depression	*proxy report* ↓ · more overall behavioural problems, more anxiety and internalising behaviour *self-report* ↔ · overall fear and anxiety within norms · increased fear of injury and medical fear *associations:* · more behavioural problems in cyanotic than in acyanotic children · maternal anxiety associated with mothers' perception of behavioural problems, and the self-perception of fear in their child	8
10	Hövels-Gürich 2002 Germany	60 (77) 78%	TGA	no exclusion	not reported mean: 10.5 yrs	> 2 yrs *	norms	pre-, peri-, postoperative data; language deficits	behaviour QoL	*proxy report* ↓ · more overall behavioural problems, more internalising and externalising behavioural difficulties *self-report* ↔ · QoL within norm *associations:* · peri-and postoperative cardiocirculatory insufficiency related to internalising and externalising difficulties, and attentional deficits · severe preoperative hypoxia, a longer DHCA related to reduced psychosocial outcome · longer CBP related to reduced QoL · expressive language deficits correlated with overall behavioural difficulties	9
11	Kamphuis 2002 Netherlds.	76 (58) 88%	TGA VSD PA other	anatomical corrective surgery; learning disabilities; language	mean: 2.2 yrs mean: 24.3 yrs	15 yrs +	norms	physical capacity	QoL	*self-report* ↓ · gross motor functioning and vitality reduced · physical functioning, physical role functioning, vitality, general health perception impaired *associations:* · subjective health related to physical status	8

Table 4.1: continued

	study origin	N (% male) response	CHD	exclusion criteria	surgical age follow up age	follow up interval	controls	assessed risk factors	outcome	results	rating (0-12)
12	Karl 2004, Australia	74 (not reported) 40%	TGA	complex TGA	median: 9 days/ median: 9.1 yrs	> 2 yrs *	"best friend" controls		behaviour	*proxy report, parents* ↓ · parents: overall competence reduced, more behavioural difficulties *proxy report, teachers* ↓ · more withdrawal, restlessness and inattention · more difficulties in speech, language comprehension and expression, more learning difficulties · social functioning within norm	8
13	Kern 1998 USA, New York	14 (57) 100%	HLHS	< 2 surgical stages	mean: >8 days/ mean: 4.4 yrs	2.8 yrs	norms; siblings	no. of heart surgeries; operative age; stage 1CBP time; stage 1 CA time	behaviour	*proxy report* ↓ · reduced daily functioning, communication, social skills, and motor abilities *associations:* · no associations between behaviour and peri-operative data	8
14	Mahle 2000 USA, Philadelph.	28 (not reported) 82%	HLHS	interrupted aortic arch; heterotaxy	< 1 month*/ mean: 8.9 yrs	> 2 yrs *	none		behaviour	*proxy report* ↓ · 50% with significant behavioural difficulties · most difficulties with attention and anxiety/ depression	6
15	Mussato 2005 USA, Wisconsin	182 (not reported) 43%	TGA DILV HLHS CAT TF AS	no exclusion	infancy/ mean: 8.7 yrs	3.7 yrs	norms; norms of chronic ill	number of heart surgeries; age; SES	QoL	*proxy report* ↓ · lower overall QoL, physical, emotional, social, and educational functioning · better overall QoL, physical and emotional functioning compared to chronically ill children *associations* · QoL not related to SES, the number of heart surgeries · positive relation between age at assessment and QoL · more complex defects with lower QoL	5
16	Oates 1994 Australia	168 (not reported) 87%	TGA TF VSD ASD	neurological, intellectual impairment	means: TGA: 0.6 / 10.1 yrs TF: 2.3/ 10.9 yrs VSD: 1.3/ 10.7 yrs ASD: 3.4 / 10.4 yrs	4-8 yrs	matched healthy controls		behaviour	*proxy report, parents* ↓ · more behavioural difficulties, particularily within the internalising dimension · more clinically relevant behavioural disturbances · lower social compentence *proxy report, teachers* « · overall behaviour and social competence within norms	8

Table 4.1: continued

	study origin	N (% male) response	CHD	exclusion criteria	surgical age follow up age	follow up interval	controls	assessed risk factors	outcome	results	rating (0-12)
22	Utens 1998 (b) Netherlds[2]	144 (59) 87%	ASD VSD TGA TF PS other	Trisomy 21	< 15 yrs/ mean: 12.6 yrs	11.9 yrs	none	medical history; peri-, post-operative data; extracardiac comorbidities; gender; age	behaviour	*associations:* · behavioural and emotional difficulties correlated with the number of heart operations · DHCA inversely related to behavioural and emotional adjustment · heart defect and extracardiac comorbities not related to adjustment	9
23	Visconti 2002 USA, Boston[1]	at 1 yr: 143 (75) 92% at 4 yrs: 152 (76) 97%	d-TGA	congenital and extracardiac anomalies; birth weight < 2500 g	mean: < 3 months/ mean: : at 1 yr and at 4 yrs	1st: 1 yr 2nd: 4 yrs	norms	parental distress; social support	behaviour	*proxy report* ↔ · overall and externalising behaviour within norms · less internalising behaviour *associations:* · early parental distress predicts behavioural adjustment when child is aged 1 and 4 yrs · no effect for social support	10
24	Walker 2002 UK	47 (51) 54%	TF	chromosomal anomaly	mean: 3.7 yrs/ mean: 23.3 yrs	19.6 yrs	insignificant VSD	repair technique; CPB duration; time of surgery	QoL; psychological profile	*self-report* ↔ · QoL and psychological profile within norms · greater need for special education *asscociations:* · no effect of surgical technique, CPB duration or time of surgery	5
25	Wright 1994 Australia	29 (69) 76%	TGA TF	non-cardiac malformation	mean: 10 mths/ mean: 9.5 yrs	not reported	norms; innocent murmur; spontaneous closure		behaviour	*proxy report, parents* ↓ · parents: maladjustment rate above norms · internalising, externalising, overall behaviour within norms *proxy reports, teacher* ↔ · teachers: behaviour within norms	9

[1]Boston cohort study; [2] Rotterdam cohort study

* estimaed

abbreviations of CHD diagnoses : AS - aortic stenosis; ASD - atrial septum defect; CAT - common arterial trunk; DILV - double inlet ventricle; HLHS - hypoplastic-left heart syndrome; d-TGA - d-transposition of the Great Arteries; PA - pulmonary atresia; PS - pulmonary stenosis; TF - Tetralogy of Fallot; TGA - transposition of the Great Arteries; VSD - ventricle septum defect

abbreviations for control groups: ADHD - attention deficit and hyperactivity disorder; FSV - functional single ventricle; JRA - juvenile rheumatoid arthritis;

abbreviations for risk factors: CA - circulatory arrest; CBP - cardiopulmonary bypass; DHCA - deep hypothermic circulatory arrest; IQ - intelligence quotient; SES - socioeconomic status

Table 4.2: Standardised instruments used in studies assessing psychological functioning and QoL in CHD after open-heart surgery

Instruments	Studies using instruments (study no.)
Psychological adjustment - semi-structured interviews	
Child Assessment Schedule (CAS)	3
Child Behavior Problems Interview (CBPI)	1
Psychological adjustment - proxy report measures	
Behaviour	
Child Behavior Checklist (CBCL)	2; 3; 8; 9; 10; 12; 14;16; 19; 23; 22; 25
Vineland Adaptive Behavior Scales (VABS)	8; 13
Teacher's Report Form (TRF)	12; 16; 25
Mental Health	
Child Health Questionnaire, parent form (CHQ-PF)	6
Psychological adjustment - self-report measures	
Behaviour	
Young Adult Self Report (YASR)	21
Youth Self Report (YSR)	18; 19
Mental Health	
Child Health Questionnaire (CHQ)	4
Duke Health Profile (DHP)	17
Mood and Anxiety	
Child Depression Inventory (CDI)	9
Revised Children's Manifest Anxiety Scale (R-CMA)	9
Revised Fear Survey Schedule for Children (R-FSSC)	9
State-Trait Anxiety Inventory (STAI)	18
Personality	
Dutch Personality Questionnaire (DPQ)	20
Frankfurt Scales of Self Concept (FSKS, German)	18
High School Personality Quesionnaire (HSPQ)	18
I Think I Am Scale (ITIAS)	1
Quality of life	
Health Utility Index	24
Inventory for the Assessment of the QoL in Children and Adolescents (IQLC)	10
Lindström Model of QoL (LMQL)	7
Pediatric QoL Inventory (PedsQL)	15
Short Form Health Survey (SF 36)	11
TNO-AZL Questionnaire for Adult's Health-Related QoL (TAAQoL)	11

4.5 Results

4.5.1 Psychological adjustment - clinical diagnoses

Two studies checked for psychiatric diagnoses according to the DSM-IV (APA, 1994) by means of respondent-based semi-structured interviews. Prevalence rates of psychiatric disorders for children with corrected TGA or with severe cyanotic defects amounted to 19% (Alden, Gilljam, & Gillberg, 1998) and 46% (Bjornstad et al., 1995), respectively. The observed proportion of children with CHD compares with that of other children with chronic illness, who have an estimated risk of suffering from psychological maladjustment two-fold that of children without chronic disease (Lavigne & Faier-Routman, 1992). In general, prevalence rates for psychiatric disorders in children and adolescents range from three to 18%, depending on the study approach and country of origin, with a median prevalence of 12% (Costello, Egger, & Angold, 2005). Comparing these base rates with the rates of psychiatric disorders in children with CHD reveals that children with cyanotic heart defects may be particularly vulnerable to suffering from clinically relevant forms of psychological maladjustment. It is less clear whether children with corrected malformations, such as TGA, have an increased risk of comorbid psychiatric illness.

4.5.2 Psychological adjustment - proxy-reports

The majority of parents observed more behavioural difficulties in their child than normative samples or control groups. This applied to homogeneous samples, e.g. TGA (Karl et al., 2004; Hoevels-Guerich et al., 2002), HLHS (Mahle et al., 2000; Kern et al., 1998) as well as to mixed diagnostic samples (Gupta et al., 1998; Oates et al., 1994; Wright & Nolan, 1994; Utens et al., 1993). Maladjustment was most apparent in difficulties relating to internalising behaviour (Hoevels-Guerich et al., 2002; Mahle et al., 2000; Gupta et al., 1998; Oates et al., 1994), whereas only one study reported considerable problems with externalising behaviour. Emotional adjustment was also reported to be reduced (DeMaso et al., 1990). Except for one study (Mahle et al., 2000) these reports scored almost equally in their methodological quality ratings.

Nevertheless, three studies did not detect any differences in psychological well being between children with CHD and reference groups (Dunbar-Masterson et al., 2001; Goldberg et al., 2000; Visconti, 2000). Two of them received the highest quality scores obtained across all studies, which implies a high degree of representativeness and validity of the results (Visconti et al., 2002; Dunbar-Masterson et al., 2001). As both studies report on children with d-TGA from the same institution, there may be considerable overlap in the samples. Yet another study from the same group described an even better outcome in d-TGA than in norms (Bellinger, Rappaport, Wypij, Wernovsky, & Newburger, 1997). The good outcome in TGA may be due to the excellent prospect of correcting this malformation during the first days of life enabling a near-to-normal life. Alternatively, results may be distorted by characteristics inherent to conditions within the specific medical institution.

Few studies assessed proxy-reports by teachers. Two of them failed to observe behavioural difficulties (Oates et al., 1994; Wright & Nolan, 1994). In contrast, one study reported more withdrawal behaviour and inattention, as well as language and learning difficulties, than in controls (Karl et al., 2004).

4.5.3 Psychological adjustment - self-reports

Most studies did not observe any deviation from the norm for levels of fear and anxiety (Gupta et al., 1998), self-esteem (Culbert et al., 2003; Alden et al., 1998), or behaviour (Salzer-Muhar et al., 2002). Self-perceived mental health (Culbert et al., 2003) and anxiety (Salzer-Muhar et al., 2002) was even better than expected. The latter findings are based on studies with a comparably low methodological quality score. Validity of their results may thus be restricted. Only one study observed psychological maladjustment in the form of behavioural difficulties in a sample with a large proportion of adolescent cases (Utens et al., 1993). Going through puberty may add to the difficulties in CHD. More studies covering this developmental period are needed.

Young adults with complex malformations reported levels of mental health comparable to the norm (Saliba et al., 2001). Another study observed that emotional functioning exceeded expectations based on normative data (Utens et al., 1994). As with the studies above suggesting psychological adjustment to be better than the norm, the latter study was in the lower range of the methodology ranking. In yet another study Utens and colleagues (Utens et al., 1998) observed behavioural maladjustment in their follow-up investigation, thus demonstrating stability of their results with advancing age of the sample.

4.5.4 Risk factors for psychological maladjustment

Heart defect: The diagnosis itself neither related to self- nor to proxy-reported psychological adjustment (Dunbar-Masterson et al., 2001; Saliba et al., 2001; Goldberg et al., 2000; Utens et al., 1998, 1998, 1994, 1993; DeMaso et al., 1990). Similarly, neither cyanosis (Saliba et al., 2001; Gupta et al., 1998), nor cardiac status (Alden et al., 1998) were associated with measures of self-reported psychological adjustment. In contrast, parents of children with cyanosis (Gupta et al., 1998), or with reduced physical capacity (Bjornstad et al., 1995), were more likely to report psychological maladjustment in their child. This is in line with findings relating to psychiatric diagnoses. Children in need of further surgical intervention were more likely to suffer from co-morbid psychiatric illness than children without this prospect (Alden et al., 1998) Inconsistent findings exist on the issue of non-cardiac comorbidities (Dunbar-Masterson et al., 2001; Utens et al., 1998).

Surgery: Deep hypothermic circulatory arrest appeared to relate to poorer psychological outcome than low or full flow cardiopulmonary bypass procedures (Utens et al., 1998; Bellinger et al., 1997). Additionally, the duration of deep hypothermic circulatory arrest correlated with the degree of psychological difficulties (Culbert et al., 2003; Hoevels-Guerich et al., 2002). Others did not observe an effect relating to the duration of circulatory arrest (Dunbar-Masterson et al., 2001; Kern et al., 1998). Pre- and perioperative cardiovascular insufficiency may relate to a poorer outcome. Age at the time of surgery was not related to psychological adjustment (Dunbar-Masterson et al., 2001; Kern et al., 1998), except in one study, which reported more internalising behaviour in patients with higher operative age (Utens et al., 1998). Less consensus exists as to the effect of the number of heart operations (Dunbar-Masterson et al., 2001; Kern et al., 1998; Utens et al., 1998).

Individual characteristics: While parental reports indicated that postoperative developmental delay (i.e., language and intellectual ability) represents a disadvantage for psychological adjustment (Hoevels-Guerich et al., 2002; Dunbar-Masterson et al., 2001; Bellinger et al., 1997; Utens et al., 1993; DeMaso et al., 1990), self-reported psychological well being was not associated with intelligence (Alden et al., 1998; Utens et al., 1998, 1993). Gender differences in overall psychological adjustment were not observed (Utens et al., 1998; DeMaso et al., 1990). A higher education related to better psychological outcome in young adults (Saliba et al., 2001).

Environmental characteristics: Early parental distress was found to relate to behavioural difficulties in the operated child with TGA three years later (Visconti et al., 2002). The role of parental well being is stressed further by the observation that maternal anxiety relates to self-perceived fear in the child and to proxy-reported behavioural maladjustment (Gupta et al., 1998). In contrast, early social support of the parents was not associated with long-term psychological adjustment in the child (Visconti et al., 2002).

4.5.5 Quality of life

Two studies found the QoL in children with operated CHD to be as good as the QoL in a normative sample (Ekman-Joelsson et al., 2004; Hoevels-Guerich et al., 2002). The former observation was based on self-perceived QoL, while the latter study combined self-reports and proxy-reports. In contrast, a third study, based on parental reports, observed an impaired QoL compared to norms, yet a better QoL compared to children with other chronic illnesses (Mussatto & Tweddell, 2005). As this study was rated lower in its methodological quality than the two former investigations, the overview supports the notion that there is good QoL for children with operated CHD. This may be particularly true for self-perceived QoL in the affected children.

To date, only two studies have reported on QoL in young adults. While Walker and colleagues (Walker et al., 2002) observed QoL to be comparable to the norm, Kamphuis et al. found QoL to be impaired (Kamphuis et al., 2002). As the latter study scored higher in the quality rating, the current data, although weak, suggest a reduced QoL.

As QoL is a multidimensional construct, several subdimensions were evaluated. A direct comparison between studies, however, cannot be made as different approaches to the concept of QoL were applied. One study observed a poorer outcome across all dimensions, including the physical, the emotional and the social subdimensions (Mussatto & Tweddell, 2005). In contrast, others observed many aspects to be comparable to healthy norms, but also found reduced satisfaction in several domains, for instance in activities, familial and social life (Ekman-Joelsson et al., 2004) or motor functioning and vitality (Kamphuis et al., 2002).

4.5.6 Risk factors for impaired QoL

Heart defect: Differences between diagnostic groups have not yet been evaluated. The effect of defect severity was only assessed in one study (Mussatto & Tweddell, 2005). Here parents of children with more complex malformation reported a lower QoL for their children. Likewise, Kamphuis found a positive association between current physical capacity and QoL (Kamphuis et al., 2002).
Surgery: Pre-, peri-, and postoperative variables did not relate to QoL consistently. As an exception Hoevels-Guerich et al. (Hoevels-Guerich et al., 2002) reported an inverse relationship between the duration of cardiopulmonary bypass and QoL in 10-year-old children. However, this association was not observed in adolescents (Walker et al., 2002).
Individual and environment: Neither language deficits nor socioeconomic status related to QoL (Mussatto & Tweddell, 2005; Hoevels-Guerich et al., 2002).

4.6 Conclusions and future directions

This systematic review aimed at analysing the literature on psychological adjustment and QoL in children with CHD after open-heart surgery during the last 15 years. Based on these findings we will draw our conclusions as to psychological adjustment, QoL, and associated risk factors in children, adolescents and young adults in the following section. Implications for future research will be addressed by examining the limitations of the evaluated studies and by discussing alternative research approaches. Finally, we will consider the practical implications of current research findings.

The majority of studies assessed psychological adjustment. As research on QoL in children with CHD has just begun, only a few studies were identified. Across studies there was a high degree of heterogeneity with regard to patient characteristics, sample size, response rates, comparison groups, age at the time of surgery, time elapsed since surgery and operationalisation of outcome variables. This may explain some of the inconsistencies in the findings. Also, the methodological quality varied greatly. To take the methodological approach into account, we assigned more weight to observations in methodologically sound studies, thus enabling us to identify some trends regarding long-term outcome in operated CHD.

The review revealed an increased risk of psychiatric disorders after open-heart surgery in cyanotic CHD. In the same way, proxy-reports by a majority of parents indicated more psychological difficulties, particularly internalising behaviour, in their child compared to other children. However, in children with corrected TGA parents consistently reported good psychological adjustment. Also, when considering self-reports by children with operated CHD we found that most of them showed successful psychological adjustment. With regard to health-related QoL in operated CHD, any conclusions have to be made with reservation. To date, the few existing studies suggest a good QoL in children with CHD. However, there may be differences in perception across the different types of informants. The absent assessment of QoL in adolescents with CHD does not allow us to draw conclusions for this age group. As few studies have evaluated QoL in young adults with operated CHD, it is suggested that these may experience an impaired QoL. Besides the actual direction of outcome, one of the most relevant findings of this review is the observed divergence between proxy- and self-reported measures. Cross-informant variance has frequently been reported in different clinical settings (Varni, Katy, Colegrove, & Dolgin, 1995), and may reflect differing, yet equally important, realities (Jokovic, Locker, & Guyatt, 2004).

This review further analysed risk factors for psychological adjustment and QoL. Interestingly, the specific diagnosis of a heart defect has been found to be irrelevant. Yet physical factors associated with the underlying malformation, such as cyanosis or postoperative cardiac status, may impair psychological well being and QoL. Few surgery-related events, such as the application of deep hypothermic circulatory arrest, have so far been related to psychological outcome. Developmental delay appears to be, at least for proxy-reports, another potential risk factor. Parents themselves may play an important role in the long-term adjustment of their child. Here early parental distress and increased maternal anxiety may represent an additional risk for the child.

With regard to the methodology of the reviewed studies, several limitations have been identified. Importantly, most studies applied a cross-sectional design to the assessment of psychological adjustment and QoL. Therefore, this approach did not allow the authors to describe the course of psychological adjustment or QoL in relation to open-heart surgery by comparing preoperative with postoperative status. Another limitation relates to the use of control groups. By comparing children with operated CHD with normative data or healthy controls, potential differences between these groups cannot directly be attributed to open-heart surgery itself. Nevertheless, given the potential side effects of cardiopulmonary bypass procedures, this issue needs to be addressed in future research. For this reason, the control group design should account for: *a)* the effect of living with chronic illness (Dunbar-Masterson et al., 2001; Mussatto & Tweddell, 2005), and *b)* the effect of living with CHD (cases can serve as their own controls if assessed preoperatively; or children with less severe CHD not requiring open-heart surgery (Walker et al., 2002).

With regard to exclusion criteria, the studies typically excluded patients with chromosomal anomalies and extracardiac comorbidities such as intellectual or neurological disability. Nevertheless, as CHD frequently accompanies chromosomal disorders and as neurological disability is one of the risk factors associated with open-heart surgery, their exclusion may have contributed to a bias towards a more robust sample. Less restrictive exclusion criteria and the systematic use of subgroup analysis would allow for the consideration of these children by accounting for the additional impact of extracardiac comorbidities.

Finally, there is a general weakness in the operationalisation of outcome measures. Although studies assessed psychological adjustment quite uniformly by means of the CBCL (Achenbach & Edelbrock, 1983), its frequent application does not reflect long-known shortcomings of the scale in the context of chronic disease (Perrin, Stein, & Drotar, 1991). The optimal study would therefore choose instruments which allow for a clear distinction between symptoms primarily associated with the disease and symptoms associated with consequences of the disease. Similar considerations apply to the assessment of QoL. Varni et al. defined utility criteria for instruments in a clinical paediatric setting, which also apply to the current research context (Varni, Burwinkle, &

Lane, 2005). Besides the general quality criteria, such as reliability and validity, instruments need to be user-friendly (i.e., short, clear), and sensitive to changes in QoL over time. Optimally, QoL instruments will integrate generic scales with disease-specific modules, thus taking advantage of normative data from healthy populations, as well as addressing the clinical change in disease-specific symptoms (Varni et al., 2005). This has been accomplished with the PedsQL (Varni, Burwinkle, Seid, & Skarr, 2003), which has been supplemented with a cardiac module (Uzark & Jones, 2003). This questionnaire is currently under validation (Marino, 2004). Similarly, for the adult population a cardiac module for the generic TAAQoL has been published, namely the CHD-TAAQoL (Kamphuis et al., 2004).

Another implication for future research results from the relatively low prevalence rates of CHD diagnoses. Multicentre studies are needed to increase sample size when evaluating outcomes in children with the same underlying cardiac malformation, e.g. HLHS. Alternatively, different diagnostic groups have been summarised (Mussatto & Tweddell, 2005; Utens et al., 1994). However, as the latter approach used heterogeneous samples with regard to the severity of the defect, age at surgery, postoperative course, number of surgical interventions and extracardiac comorbidities, it may not reflect effects inherent to a particular diagnosis and its prospect of correction. Furthermore, the demonstrated divergence between self-reports and proxy-reports highlights the need for outcome assessments by means of multiple informants.

Based on the findings of this review, some practical suggestions can be made for the clinical context. The evaluation of potential risk factors has identified some factors that relate either to the defect itself, to individual characteristics of the child or to their environment. Children with more severe heart defects, e.g. cyanotic defects or those in need of future surgical intervention, are more likely to suffer from comorbid psychiatric disorder or psychological maladjustment according to parental reports. In addition, QoL appeared to be impaired with more complex malformations. While all of these findings require further empirical replication, they do suggest which child is in need of preventive psychosocial intervention, namely, the physically impaired child. Furthermore, children with expressive language delay or intellectual impairment are at increased risk of experiencing proxy-reported behavioural difficulties. Here, early detection and continual support for special needs may reduce the risk of long-term behavioural difficulties. Finally, there is convincing evidence of the significance of the role that parental, particularly maternal, well being plays in mediating psychological adjustment in children with CHD. Hence, the way parents adapt to the illness of their child may be of great importance for his or her psychological well being. This calls for an integrated approach to family support, taking the child's individual needs into account as well as those of the parents.

In the face of the limited options for change within the surgical approach, new possibilities may be found in the wider scope of complementary care for fostering successful long-term psychological adjustment and QoL in children, adolescents and young adults with CHD after open-heart surgery.

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5 The physiology of stress

The following chapter explores to what extent the widely used physiological parameter cortisol can serve to elucidate effects that surgery-related experiences have on affected parents. To introduce these considerations, the general stress conception related to the context of this thesis, the physiological fundamentals of cortisol secretion and the applications in stress research are briefly outlined.

5.1 Stress-related concepts in the context of parenting a child with CHD

"*Stress may be defined as real or interpreted threat to the physiological or psychological integrity of an individual that results in physiological and/or behavioral responses.*" (Mc Ewen, 2000, p.508)

While this sentence constricts the definition of "stress" to a threat posed to the integrity of the individual, the definition may be extended by postulating that stress also occurs when the integrity of someone other than the self is compromised. For instance, severe illness in a child and associated high-risk interventions are experienced as extremely stressful by the affected parents (see Chapter 3.2.2). With regard to stimulus modality, the stress literature typically differentiates between stress stimuli of overt physical quality, such as physical exertion, extreme temperatures or noise, and stimuli of psychological quality, such as time pressure, loss of control, novelty or conflict (McEwen, 2000). Either modalities are encountered by parents of children undergoing open-heart surgery. Physical stress is imposed on parents as they may find themselves in an unfamiliar hospital environment for a long period of time with little room for physical needs, such as sleep, rest, exercise, or regular meals. The psychological stress is more apparent and has already been discussed in Chapter 3.2.2. To give an example, parents of children admitted to a paediatric intensive care unit reported feeling most distressed by the inability to protect their child, thus experiencing a great degree of loss of control (Miles, Carter, Riddle, Hennessey, & Eberly, 1989). Referring back to McEwen's definition of stress, physiological and/or behavioural responses to a stress stimulus are part of the

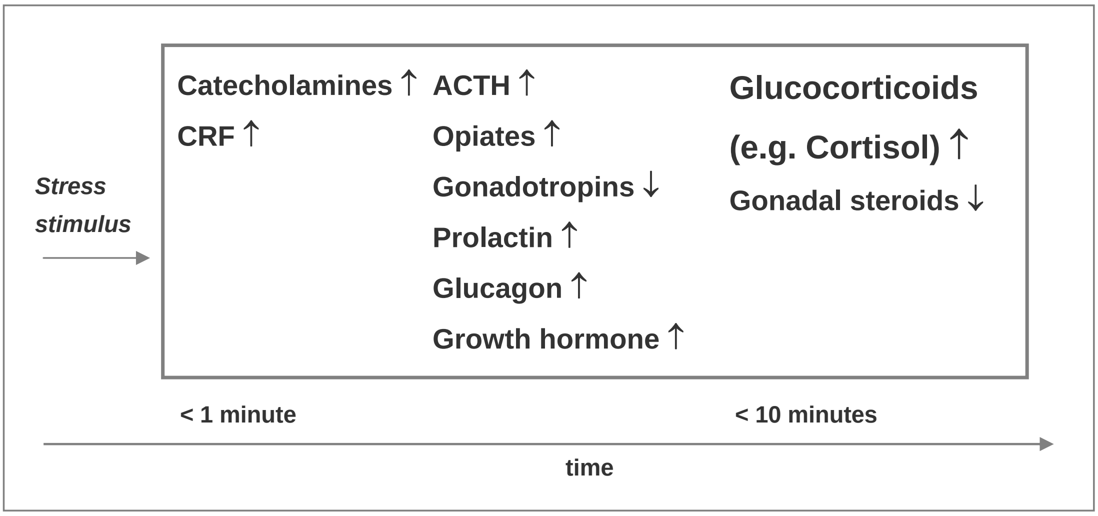

Figure 5.1: Hormonal secretory patterns of the stress response (adapted from Sapolsky et al., 2000, p.57). *Abbreviations: ACTH - adrenocorticotropic hormone; CRF - corticotropin-releasing factor*

general stress concept. Physiological correlates of acute, prolonged and traumatic stress will be considered in this chapter.

5.2 The physiological stress response

5.2.1 Endocrine regulation of acute stress

The stress response is often defined in terms of physiological changes, such as endocrine activity of the hypothalamus-pituitary adrenal axis (HPA) and activation of the sympathetic branch of the vegetative nervous system. In the following, it is described what constitutes the endocrine stress response and its physiological consequences. Since one focus of this thesis lies on the stress hormone cortisol, activities of the HPA axis are highlighted. The HPA axis is a hierarchical system, which connects the central nervous system with the endocrine system. For a general overview of the physiology of stress see (McEwen, 2000; Sapolsky, Romero, & Munck, 2000; Kirschbaum & Hellhammer, 1999).

As can be seen in figure 5.1 the first hormones are released only within seconds of the occurrence of a stressor. One of them is the hypothalamic corticotropin-releasing factor (CRF), which stimulates the subsequent release of the adrenocorticotropic hormone (ACTH) in the pituitary a few seconds later. Other rapid hormonal alterations include the release of the catecholamines adrenaline and noradrenalin from the sympathetic ner-

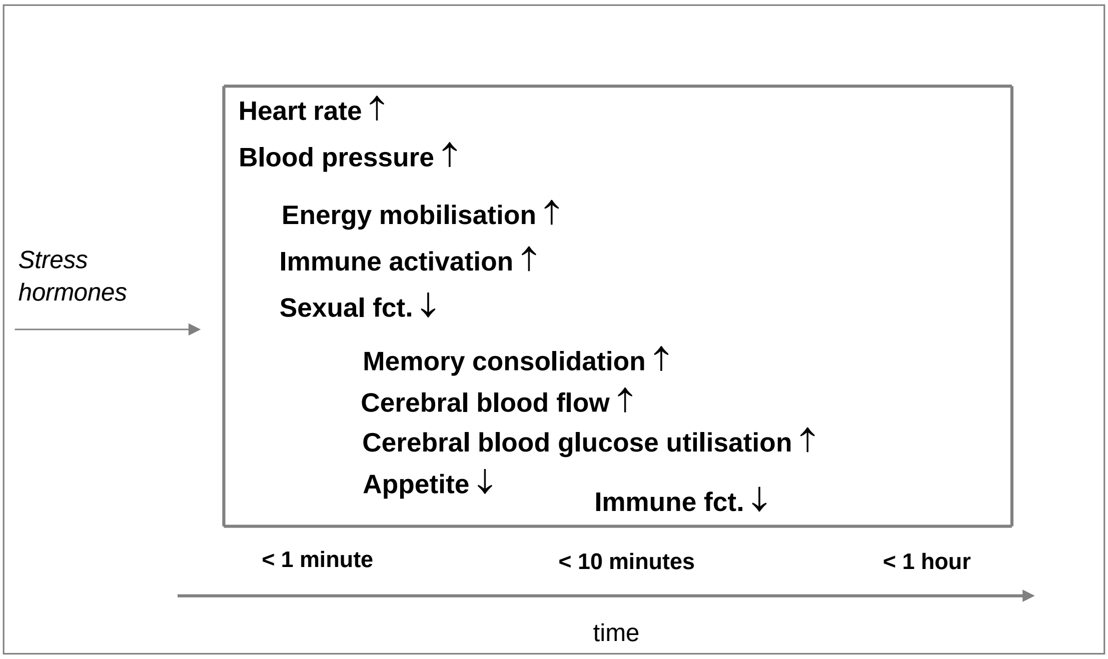

Figure 5.2: Acute physiological changes due to endocrine stress responses (adapted from Sapolsky et al. 2000, p.57)

vous system, and of prolactin and glucagon as well as a reduction in the levels of sex hormones. In a secondary, much slower surge of hormonal changes more glucocorticoids enter the peripheral blood while the release of gonadal steroids is suppressed.

The associated effects of these hormones in the target tissues are delayed relative to their time of release. The effects will last as long as hormonal bioavailability permits, governed by the physiological half-life time of the biologically active compound. Physiological changes resulting from the depicted hormonal alterations are summarized in figure 5.2. As an example, the physiological effects of the most potent glucocorticoid cortisol are outlined further: increases in cortisol secretion occur on top of basal cortisol levels with a relative time delay to a stress stimulus. The hormone's fairly long half-life ensures a mode of action for up to 110 minutes (Kirschbaum & Hellhammer, 1999). Cortisol serves the general purpose of ensuring the empowerment of the organism by mobilising energy resources and inhibiting less important bodily functions under conditions of high demand or stress. This is achieved by supporting the process of glucogenesis in the liver and restraining the consumption of glucose in body tissue, which consequently leads to a rise in blood sugar levels. Immunosuppressive action and anti-inflammation are other effects of increased cortisol. Reduced activity of the natural killer cells and the production of antibodies under acute psychological stress have been observed (Schedlowski et al., 1993), as well as differential marginalisation of immune-competent cells to sites of potential injury (Dhabhar, 2003). Finally, cortisol acts in a protective way by preventing the organism from overshooting and from damaging stress reactions. This is accomplished by suppressing other mediators of the stress response (Munck & Naray-Fejes-Toth, 1992). Thus, cortisol secretion and the release of other hormones promote adaptation to acute stressors enabling the body to cope appropriately with changes in the internal or external environment.

5.2.2 The hypothalamus-pituitary-adrenal axis

Cortisol has been described as one of the important physiological stress mediators in the adaptation of the organism to a stressful event (Chapter 5.2.1). The stress hormone is the end-product of a cascade of events initiated by stress-induced activation of the hypothalamus. Figure 5.3 schematically depicts components and mechanisms of the HPA axis. For reasons of simplification only the main mechanisms are considered, although numerous inhibiting and stimulating transmitter substances affecting HPA activity are released at distinct levels (for an overview see Kirschbaum & Hellhammer, 1999). As illustrated in figure 5.3 the HPA axis is a hierarchical hormone system consisting of the hypothalamus, the anterior pituitary gland, and the adrenal cortex. Upon nerval stimulation CRF is released from hypothalamic neuroendocrine cells targeting the CRF receptors of the corticotropes in the anterior pituitary gland. Subsequently ACTH is released from the pituitary into the circulation. ACTH acts upon receptors in the adrenal cortex, thus stimulating the production and the secretion of glucocorticoids, amongst them cortisol. Negative feedback mechanisms down-regulate the synthesis and the secretion of CRF and ACTH via the stimulation of mineralocorticoid and glucocorticoid receptors at the level of the pituitary and the hypothalamus.

The illustrated rise in CRF, ACTH, and cortisol, in response to acute stressors occurs on top of basal hormonal levels, which exhibit circadian rhythmicity.

5.3 The circadian rhythm of cortisol secretion

Humans with a regular sleep-wake cycle (i.e., sleeping at night, activity during the day) exhibit characteristic circadian variation in their 24-hour cortisol secretion (Liu, Kazer, & Rasmussen, 1987; Weitzman et al., 1971). This circadian rhythm implies maximum levels in the morning with a peak approximately 30-45 minutes after awakening and a

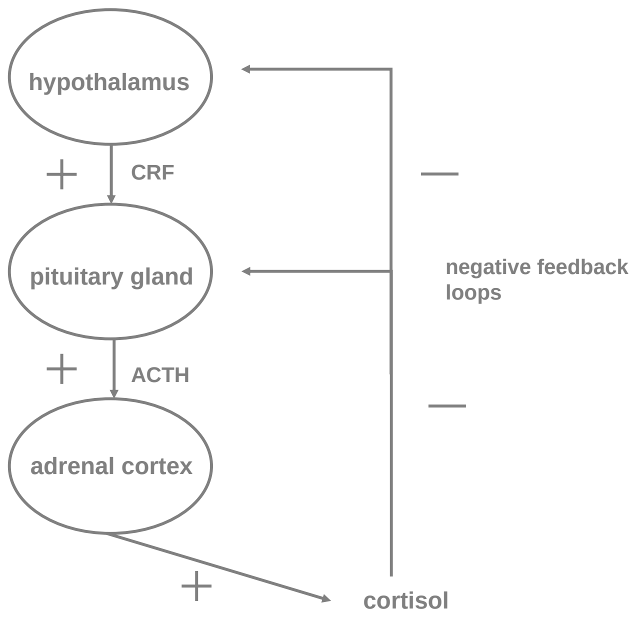

Figure 5.3: Schematic description of stress-induced HPA activity.

subsequent continual decline in secretory levels reaching a nadir at night (Edwards, Clow, Evans, & Hucklebridge, 2001). The characteristic morning rise in cortisol has frequently been termed the cortisol response to awakening, yet its physiological significance remains to be elucidated. Nevertheless, it is considered a discrete and distinctive part of the cortisol circadian cycle (Clow, Thorn, Evans, & Hucklebridge, 2004).

Dysregulation in diurnal cortisol secretion has frequently been associated with psychopathology and also with physical disorder, for instance in major depression and PTSD (Yehuda, Teicher, Trestman, Levengood, & Siever, 1996), in fibromyalgia (Griep et al., 1998), or in cancer-related fatigue (Bower et al., 2005). The characteristic morning rise has been observed to be particularly sensitive to stress-related phenomena. Thus, elevated morning cortisol levels were observed in self-reported chronic worrying and social stress (Wuest, Federenko, Hellhammer, & Kirschbaum, 2000), in female burnout patients (Grossi et al., 2005), and in stress due to unemployment (Ockenfels et al., 1995). It is unknown whether the observed alterations in cortisol secretion mediate associations between chronic stress and health-related difficulties (Kivimaki et al., 2002; von Kaenel, Mills, Fainman, & Dimsdale, 2001). While the rise in cortisol levels in response to an acute stressor serves an adaptive purpose, enduring changes in cortisol secretion may be maladaptive (McEwen, 2000). Consequently, further studies are needed that prospectively investigate the course of diurnal cortisol secretion in healthy humans who are exposed to prolonged or chronic stress.

5.4 Cortisol secretion during prolonged, chronic and traumatic stress

Few studies have investigated cortisol secretion in humans who have experienced prolonged or chronic stress. These studies included stressors of varying intensity, duration and emotional impact, such as exposure to war (Zarkovic et al., 2003; Weizman et al., 1994), long-term unemployment and job insecurity (Ockenfels et al., 1995; Arnetz et al., 1991), caring for a demented spouse (Bauer et al., 2000) or parenting a child with end-stage malignant disease (Friedman, Mason, & Hamburg, 1963). Exposure to war was observed to significantly suppress cortisol levels in healthy civilians in one study (Zarkovic et al., 2003) but not in another investigation (Weizman et al., 1994). The behavioural and psychological symptoms in dementia patients are a major source of stress for their carers (Vugt et al., 2005). With regard to cortisol profiles, elevated overall cortisol levels have been observed in these carers (Da Roza Davis & Cowen, 2001; Bauer et al., 2000; Vedhara et al., 1999) as well as increased awakening cortisol levels (Vugt et al., 2005). In contrast, a very early study reported elevated HPA activity in the parents of children with cancer only when the parents were exposed to extreme levels of psychological distress (Friedman et al., 1963). As the latter study did not compare HPA activity with a control group but only within the group of parents, a conclusion regarding general alterations in HPA activity of parents of children with a life-threatening illness cannot be made. Comparison across studies is hampered by the difference in age, methodological approach and stressor duration. Also, there may be different degrees of psychological traumatisation associated with the stressors investigated.

Victims of traumatisation who suffer from chronic PTSD show suppressed levels of cortisol. To give an example, the mothers of childhood cancer survivors with illness-related PTSD were found to secrete lower 12-hour overnight urinary cortisol than mothers who did not develop PTSD related to their child's cancer (Glover & Poland, 2002). The repeatedly described finding of lowered cortisol levels in PTSD suggests a hypersensitivity of the HPA axis to the negative feedback regulatory loop. It has been postulated that an increase in the number and the sensitivity of glucocorticoid receptors at the pituitary lead to a lowered cortisol response to HPA activation in PTSD (Yehuda, 1998). However, it unclear whether the hypersensitive HPA axis in PTSD is a consequence of the development of PTSD itself, or whether HPA alterations preceded the disorder and thus, determined the biological response to traumatic stress.

Taking all findings together, the physiological reaction to acute stress is an adaptive response serving to maintain the organism's homeostasis. Cortisol is a prominent mediator of endocrine stress regulation. In contrast to regulatory mechanisms in response to acute stress, less is known about circadian cortisol secretion during exposure to prolonged stress. Nevertheless, it has been suggested that long-term alteration in cortisol activity may be maladaptive (McEwen, 2000). Thus, parents of children with CHD undergoing open-heart surgery may be exposed to prolonged stress accompanied by alterations in cortisol levels. With regard to the development of symptoms of posttraumatic stress, there may be a biological vulnerability in some parents, characterised by a pre-existing alteration in HPA activity. This thesis may contribute to support such statements that so far have received little or no research attention within this context.

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6 Hypotheses and general study approach

6.1 General questions

The present empirical study had, above all, one general aim, namely, to elucidate the effects of open-heart surgery in a child with CHD on affected parents. As discussed in Chapter 3 parents of children with CHD are at an increased risk of suffering from psychological maladjustment, for instance by experiencing heightened levels of parenting distress (Uzark & Jones, 2003) or symptoms of psychopathology (Rona, Smeeton, Beech, Barnett, & Sharland, 1998). The event of cardiac surgery in the child may be experienced as particularly threatening, eliciting increased levels of anxiety and psychological distress before and after surgery (Wray & Sensky, 2004; Utens et al., 2000). To current knowledge, the presence of symptoms of surgery-related PTSD has not been evaluated in parents of children undergoing open-heart surgery. Neither have objective physiological markers of the prolonged stress experience been previously assessed in this cohort. Consequently, this thesis aimed at evaluating the extent to which parents of children with CHD undergoing open-heart surgery show deviations in their diurnal cortisol secretion and whether they experience surgery-related symptoms of PTSD after their child's discharge from hospital. The study also aimed at identifying possible predictors of the severity of symptoms of posttraumatic stress, including possible alterations in HPA activity in the affected parents. Thus, the following hypotheses were made.

6.2 Specific Hypotheses

6.2.1 Diurnal cortisol secretion in parents of children undergoing open-heart surgery

The hypotheses regarding cortisol secretion in parents of children undergoing open-heart surgery are, in part, based on the evidence presented in Chapter 5. Although findings regarding cortisol secretion under prolonged stress exposure are inconsistent, studies investigating carers of dementia patients rather consistently found elevated overall cortisol secretion (Da Roza Davis & Cowen, 2001) and elevated levels upon awakening (Vugt et al., 2005). Apart from the differences in patient characteristics, it is uncertain whether these findings also apply to carers of a younger age, namely, the parents of children with CHD. Very early evidence suggested elevated HPA activity in parents of children with malignant disease when experiencing extreme levels of psychological distress (Friedman, Mason, & Hamburg, 1963). Thus, the following hypotheses were derived:

- Parents of children undergoing open-heart surgery experience severe and prolonged levels of chronic stress. Therefore, they generally have higher overall diurnal cortisol levels compared to parents of children without CHD.
- Open-heart surgery in one's child is a threatening experience. Therefore, parents show markedly increased cortisol secretion superimposed on the resting-day levels on the actual day of surgery.
- Morning cortisol levels, i.e. levels immediately after awakening, and the morning rise in cortisol levels in the first 30-45 minutes after awakening, are particularly sensitive to prolonged as well as to acute levels of stress. Parents of children undergoing open-heart surgery show higher morning cortisol levels compared to parents of children without CHD. More specifically, a steeper morning rise after awakening is hypothesised. Again, effects are postulated to be most pronounced on the day of surgery.

Furthermore, it was of interest to assess whether indices of the perioperative course in the child, i.e. the duration of surgery and the surgical risk, differentially affect parental HPA activity. In the face of missing evidence the null hypothesis was tested:

- Perioperative data of the child characterising the duration of the intervention and its estimated surgical risk are not associated with changes in cortisol secretion in parents on the day of surgery.

Finally, it was examined whether psychological characteristics of the parents, such as preoperative levels of anxiety or depressive mood, and subjective stress perception, are related to their cortisol secretion on the day of surgery. Commonly, heightened levels of negative affect have been found to relate to cortisol secretion (Zobel et al., 2004). Thus, it was hypothesised:

- Higher levels of preoperative anxiety and depressive mood relate to increased cortisol secretion in parents on the day of surgery. Furthermore, the subjective perception of stress is positively associated with parental cortisol levels.

6.2.2 Acute symptoms of posttraumatic stress in parents of children undergoing open-heart surgery

Considering the findings presented in Chapter 3 the current study tested the following hypotheses:

- Parents of children with life-threatening conditions have been shown to be at increased risk of experiencing illness-related posttraumatic stress. Therefore, parents of children undergoing open-heart surgery experience higher levels of posttraumatic stress after their child's discharge from the hospital than the average population. The incidence rate for surgery-related symptoms of acute PTSD is higher in these parents than in the general population.

With regard to risk factors for PTSD, characteristics of the traumatic event itself, gender, socioeconomic background, social support, and pretraumatic levels of psychological adjustment have been found to increase vulnerability to PTSD in victims of traumatisation (Brewin, Andrews, & Valentine, 2000). Exploring whether these findings can be applied to the population of parents of children with CHD undergoing open-heart surgery, it was hypothesised:

- Pre-, peri- and postoperative data of the child that indicate a more severe heart defect, a higher surgical risk, and a more complicated postoperative course predict more severe levels of acute surgery-related posttraumatic stress in parents. Personal characteristics, such as being female, coming from a lower socioeconomic background, receiving little social support, and suffering from preoperative psychological maladjustment, also increase the risk of suffering from more severe symptoms of surgery-related posttraumatic stress.

Given the scarcity of prospective data regarding the relationship between pretraumatic cortisol secretion and the experience of symptoms of posttraumatic stress, the null hypothesis was tested:

- Characteristics of pre-surgical cortisol secretion in parents do not predict acute levels of surgery-related posttraumatic stress in parents after discharge of their child from hospital.

6.3 Study approach

6.3.1 Clinical context

Since January 2004 open-heart surgery under use of the heart-lung machine has been performed on children with CHD on a daily basis at the Children's Hospital of the University of Zurich. The hospital has since established itself as a well-recognised centre of competence for paediatric cardiosurgery. Besides the obvious intention of correcting inborn malformations of the heart, another major aim is to ensure a good QoL for the operated children and their families. In order to systematically assess the outcome in all patients seen within the cardiosurgical context, a prospective cohort study has been initiated. The study follows two major aims:

- to prospectively assess the neurodevelopment and the QoL of all children with CHD aged from 0 to 16 years before and after open-heart surgery with the heart-lung machine; and
- to prospectively assess the psychological adjustment and QoL of the parents of these children before and after surgery.

The current thesis focuses on the latter part of the study. Thus, the following details are restricted to the assessment of parents of children with CHD undergoing open-heart surgery.

6.3.2 Study design

Figure 6.1 provides a schematic overview of the study design as originally developed in the planning phase. As the schema illustrates, psychosocial characteristics were assessed by means of standardised questionnaires before surgery, after discharge of the child from hospital, as well as six and twelve months after surgery. In addition, parental cortisol secretion was assessed on a preoperative resting day, on the actual day of surgery and on a resting day after the child's discharge from hospital. However, during the pilot phase of the study, it became apparent that not all parents would be able to fill in a standardised questionnaire prior to the child's surgery. Reasons were either time constraints, as in the case of emergency operations, demanding job and family responsibilities, or, understandably, extreme emotional distress. Not surprisingly, such parents were also unable to comply with the cortisol sampling protocol. Thus, the following amendments were made to the original study design: Preoperatively, parents were only included if there was sufficient time to answer an extensive questionnaire, e.g., in the case of elective surgery, and if the parents appeared emotionally stable.

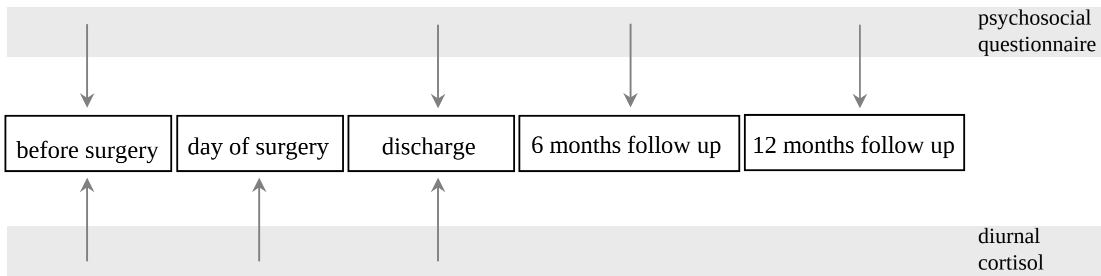

Figure 6.1: Design of the prospective cohort study.

The recruitment of parents was extended to the follow-up assessment after the child had already been operated on. Although, the preoperative information on psychosocial characteristics was missing in these cases, it was decided that inclusion of these parents would contribute to a better understanding of psychosocial outcome in all parents after open-heart surgery in their child. The assessment of cortisol secretion was also restricted to a subgroup of parents of children undergoing elective surgery. Ethical considerations relating to the surgical risk for the child led to a further restriction of the inclusion criteria. Only parents of children with a small to moderate surgical risk were approached for assessment of cortisol secretion. Detailed inclusion and exclusion criteria for the study will be presented in the respective empirical chapter.

The present thesis is restricted to the acute phase of the study starting before the event of open-heart surgery and ending after discharge of the child from hospital, as the six- and the twelve-months follow up still awaited completion.

6.3.3 Implementation of the study

In order to ensure smooth organisation, a study coordinator was employed who was responsible for coordinating recruitment and follow-up assessments as well as for the data collection from medical records. The study coordinator was also the first contact person for participating parents. Procedures as to the recruitment and follow-up assessments will be described in detail in the respective empirical chapters.

6.3.4 Data management and statistical analyses

The questionnaire data were entered into a FileMaker database (FileMaker Pro 7, Unterschleissheim). In order to prevent input error, each set of data was entered twice with automated error detection. For statistical analyses data were imported into SPSS 11.0 (SPSS, Chicago, IL), SAS 8.2 (SAS, Inc., Cary, NC), and MLWin 2.02 (Centre for Multilevel Modelling, Bristol). Analyses of the cortisol data were performed using multilevel modelling as suggested by Hruschka (Hruschka, Kohrt, & Worthman, 2005). Questionnaire data were predominantly analysed applying the general linear modelling approach. Exact details will be given in the respective chapters.

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7 Circadian cortisol secretion in parents experiencing open-heart surgery in their child - a longitudinal repeated measure analysis

7.1 Abstract

Objective: To assess the effects of prolonged stress on the activity of the HPA axis in healthy parents before, during and after open-heart surgery in their child. Further, to evaluate potential associations between perioperative events and parental cortisol secretion. Finally, to test whether state and trait measures of anxiety, depressive mood, and the subjective stress perception relate to cortisol levels on the day of surgery.

Methods: A cohort of 57 healthy parents of children with CHD collected saliva samples on a typical resting day before surgery, on the actual day of surgery, and on a typical resting day after their child's discharge from hospital. Basal HPA activity was assessed by examining awakening cortisol and diurnal cortisol profiles. Parents completed standardised questionnaires assessing psychological variables before the child's admission to hospital. Multilevel analysis was used to analyse differences between the study sample and a reference group of working parents. Perioperative data and psychological variables were included in the multilevel approach.

Results: Overall cortisol secretion in parents was markedly elevated on the day of surgery and showed a trend towards higher levels on the resting day after the child's discharge compared to the reference sample. Cortisol levels immediately after awakening before the day, on the day, and after the day of surgery were higher than awakening cortisol in the reference sample. A marked increase in the cortisol morning rise in parents was only observed for the day of surgery. The differences between the day of surgery and resting days were explained to a large extent when entering variables characterising the perioperative course, and most importantly the subjective stress perception at sampling. In contrast, trait anxiety and depression were unrelated to cortisol secretion rates.

Conclusion: The event of open-heart surgery in a child may contribute to enduring changes in HPA activity in healthy parents; this is mainly reflected in the heightened levels of cortisol immediately after awakening. Cortisol secretion under acute psychological stress on top of prolonged stress exposure may result in a marked morning rise and

a tonic shift in the activity of the HPA axis towards higher cortisol secretion throughout the entire day.

7.2 Introduction

The physiological reaction to acute stress is an adaptive response. It serves to maintain the organism's homeostasis in a changing and challenging environment (McEwen, 2000). Endocrine stress responses are mediated in part by the activity of the HPA axis. Thus, the stress response results in a marked rise in cortisol secretion, which is superimposed upon the basal circadian secretion pattern. The latter is characterised by a morning peak about 30-45 minutes after awakening and a subsequent decline towards the nocturnal nadir (Pruessner et al., 1997). Downstream effects of cortisol secretion include changes in cardiovascular, metabolic, and immunological systems aiming at maintaining homeostasis in vital parameters. The acute stress response of healthy individuals is a well orchestrated response of biological systems, in which cortisol is believed not only to participate in stimulation, but also in protecting the organism from overshooting and damaging stress reactions (Munck & Naray-Fejes-Toth, 1992).

In contrast to the acute adaptive response, prolonged stress may have detrimental effects. Converging support exists for the hypothesis that there is an association between chronic stress and various health problems (Kiecolt-Glaser et al., 2003; Kanel, Dimsdale, Patterson, & Grant, 2003; Kivimaki et al., 2002). However, less is known about the underlying biological mechanisms linking chronic stress to the onset or the course of disease. Dysregulation of the HPA axis has been observed in various forms of psychopathology and in physical disorders (Bower et al., 2005; Griep et al., 1998; Yehuda, Teicher, Trestman, Levengood, & Siever, 1996), pointing to the possible role of cortisol in mediating this association. Currently, there is a scarcity of data on the regulation of the HPA axis in healthy adults exposed to chronic stress, e.g., periods of intense psychosocial strain that persist for several days.

The existing data on HPA activity in chronically stressed individuals remains inconclusive. Previous investigators either followed an observational approach by studying the effects of prolonged stressors on cortisol secretion or they employed cross-sectional techniques correlating the degree of perceived chronic stress with concurrent measures of HPA activity. The former type of studies, for example, investigated the activity of the HPA axis in subjects exposed to war (Zarkovic et al., 2003; Weizman et al., 1994), unemployment (Ockenfels et al., 1995; Arnetz et al., 1991), caring for a demented spouse (Vugt et al., 2005; Da Roza Davis & Cowen, 2001; Bauer et al., 2000; Vedhara et al., 1999) or having a child with a life-threatening illness (Friedman, Mason, & Hamburg, 1963). The majority of these studies support the notion that there is an altered cortisol secretion under chronic stress, but little consensus exists as to the direction of change. While research on caregivers of dementia patients usually finds elevated overall cortisol levels (Da Roza Davis & Cowen, 2001; Bauer et al., 2000; Vedhara et al., 1999) and increased morning levels directly after awakening compared to controls (Vugt et al., 2005), studies with subjects from the healthy middle-aged population either observed an elevation (Ockenfels et al., 1995), no apparent deviations (Weizman et al., 1994) or reduced overall levels of cortisol (Zarkovic et al., 2003). Data on morning cortisol levels show even larger heterogeneity (Schulz, Kirschbaum, & Pruessner, 1998; Ockenfels et al., 1995). Moreover, a comparison of the various studies is impeded by systematic differences in sampling method and sampling times.

The second approach employing correlational techniques has yielded more consistent results. Positive associations between morning cortisol levels and perceived chronic stress were repeatedly demonstrated (Steptoe, Cropley, Griffith, & Kirschbaum, 2000; Wust, Federenko, Hellhammer, & Kirschbaum, 2000; Pruessner, Hellhammer, & Kirschbaum, 1999; Schulz et al., 1998). However, the cross-sectional nature of these studies does not permit any causal inference. Therefore studies are needed, which prospectively investigate HPA axis activity in healthy subjects exposed to chronic stress. Such studies might help to elucidate the effects of superimposed chronic stress on the diurnal cortisol secretion in otherwise healthy individuals.

Parents of children with cancer or CHD represent a population of healthy adults, who are exposed to worry and fear over a long period of time. The illness and associated treatments pose a serious threat to the physical integrity of their child, including the possibility of death. Underscoring the ecological validity of this situation as a severe stressor, the increased prevalence of PTSD parents of children with a life-threatening or chronic disease has been documented (Landolt, Vollrath, Laimbacher, Gnehm, & Sennhauser, 2005; Kazak et al., 2004; Young et al., 2003). This may be accompanied by long-term changes in endocrine regulation (Glover & Poland, 2002). The landmark study by Friedman and co-workers provided early insights into HPA axis regulation under such chronic stress exposure (Friedman et al., 1963). Using the state-of the art method available at the time, the investigators observed relatively stable urinary 17-hydroxycorticosteroid levels in parents of children with neoplastic disease throughout hospitalisation. However, pronounced hormonal increases were observed at admission and when parents experienced extreme levels of psychological distress. So far, similar work using the modern and less cumbersome sampling technique of salivary cortisol measurements has not been conducted (Kirschbaum & Hellhammer, 1989).

Parents of children undergoing open-heart surgery experience comparable psychological strain, as do parents of children with cancer. The psychological impact of the surgical correction of CHD on affected parents has previously been demonstrated (Wray & Sensky, 2004; Utens et al., 2000). Open-heart surgery implies a predictable sequence of stressful events: the waiting period before surgery, the day of surgery and the subsequent hospitalisation in an intensive care unit. Altogether this sequence qualifies as a prolonged field stressor in the sense that it involves anticipatory fear, a sense of uncontrollability, and physical strain. Using circadian salivary cortisol sampling, we aimed at elucidating the effects of this chronic stressor on diurnal HPA axis excretion including the characteristic morning rise.

We hypothesised that, as a result of the prolonged stress exposure, the circadian cortisol secretion would be generally elevated in parents of children with CHD compared to parents with children without CHD. As the morning rise, often interpreted as the cortisol response to awakening (Clow, Thorn, Evans, & Hucklebridge, 2004) has been shown to be particularly sensitive to stress, we further expected a more pronounced morning rise in cortisol levels after awakening. Based on Friedman's observations, we hypothesised that the elevation in overall cortisol levels would be most pronounced on the day of surgery (Friedman et al., 1963). Moreover, we expected the morning rise after awakening to show the highest increase on the day of surgery, reflecting an anticipatory reaction to the perceived threat to the child. Additionally, we aimed at exploring whether patterns of circadian cortisol secretion on the day of the child's surgery relate to the surgical risk and the duration of surgery. With regard to psychological characteristics, we postulated that pre-operative trait anxiety and depressive mood, as well as subjective stress perception during the day of surgery are associated with perioperative cortisol secretion.

7.3 Method

7.3.1 Participants

The present study is part of an ongoing prospective cohort study repeatedly assessing psychological adjustment and long-term adjustment in parents before and after open-heart surgery on their child for correction of CHD. Parents are recruited at the Children's Hospital of the University Zurich, Switzerland. The overall objective of the study is to identify risk and resiliency factors in the psychological well-being of affected parents. Here we report on a subsample, which collected salivary samples for cortisol analyses. A total of 57 parents (47.4% males) of 33 children with CHD scheduled for elective open-heart surgery took part in the study between August 2004 and December 2005. Parents were of Caucasian origin and in good health according to a) self-reported symptoms of acute infection or disease and b) self-reported history of chronic medical illness or psychiatric disorder. Table 7.1 gives an overview of the characteristics of the children of the parents investigated in this study.

In general, every parent of a child scheduled for elective open-heart surgery was potentially eligible. During the pilot phase we approached every consecutive parent for enrolment. This procedure revealed that a large proportion of parents was overwhelmed by the emotional distress of the situation. Often parents were unable to partake in a semi-structured interview, let alone complete a questionnaire or comply with a salivary sampling protocol. After consulting with the ethics committee, we applied the following restraints: Parents were not included, if 1) the child had a surgical risk score of > 4 according to the RACHS-1 risk stratification (range 1-6, 6 indicating the highest risk) (Jenkins et al., 2002); 2) there was known emotional instability with associated risk of psychological decompensation; 3) recent serious traumatic life events had occurred; 4) they lived in socially adverse circumstances. Thus, the sample is biased towards parents showing less acute strain. Additional formal exclusion criteria were 5) insufficient command of the German language, 6) current pregnancy or recent delivery of a child, and 7) recent use of glucocorticoid drugs. Women taking oral contraceptives were included (n=1).

Recruitment was carried out as follows: Parents were approached by a study coordinator several weeks prior to surgery and given written information on the study. Parents who expressed interest were met during a pre-surgical medical examination of their child. They provided informed consent and received preoperative questionnaires together with purpose-designed salivary cortisol sampling kits. No incentive was offered except for feedback on individual cortisol profiles and on study results. The study was approved by the Ethics Committee of the Children's Hospital of the University Zurich.

Reference sample A reference sample of working parents from the manufacturing industry was selected from the database of a previous study by our group, using the same salivary sampling protocol and the same analytical assay (Kudielka et al., 2005). These individuals had collected two cortisol profiles during working days and a third profile on the second of two consecutive resting days (weekend). The reference sample consisted of 77 parents (70 males) of Caucasian origin. An extensive questionnaire completed by the reference sample used identical psychometric scales to the questionnaire used in the surgery context with respect to anxiety, depressive mood, and health-related quality of life.

Table 7.1: Illness-related characteristics of children of the participating parents.

Child characteristics (n=33)	
Age in years (sd)	4.2 (4.9)
Males (%)	19 (39.4)
Known genetic defect	
Trisomy 21 (%)	4 (12.1)
Microdeletion 22 q11 (%)	3 (9.1)
Other (%)	5 (15.2)
Main diagnosis with indication for OHS	
Atrioventricular septum defect (%)	6 (18.2)
Tetralogy of Fallot (%)	5 (15.2)
Ventricle septum defect (%)	5 (15.2)
Aortic stenosis (%)	4 (12.1)
Atrial septal defect (%)	4 (12.1)
Pulmonary atresia (%)	2 (6.1)
Other (%)	7 (21.2)
RACHS-1risk stratification	
1 (%)	6 (18.2)
2 (%)	9 (27.3)
3 (%)	18 (54.5)
Extracorporeal circuit time in min, mean (sd)	138.3 (71.5)
Duration	
Postoperative intubation in days, mean (sd)	1.8 (2.2)
Intensive care in days, mean (sd)	4.3 (3.2)
Overall hospitalisation in days, mean (sd)	13.9 (8.7)

7.3.2 Procedure

Data collection comprised: a) collection of circadian cortisol profiles on a typical resting day prior to surgery, on the day of surgery, and on a typical resting day after the child's discharge from hospital, and b) completion of a standardised questionnaire prior to surgery including items on depressive mood, anxiety, and health-related quality of life.

For cortisol profiles, parents were asked to collect saliva immediately after awakening, 30 minutes post awakening, at 8.30 a.m., 11.30 a.m., 4 p.m., and 8 p.m. For each sample parents were asked to indicate the current level of subjective distress. If a sample was not obtained at the specified time, parents were asked to take a delayed sample and to record the exact sampling time. In encouraging participants to take delayed samples rather than to feign samples, we hoped to reduce the considerable effects of non-compliance on estimates of cortisol secretion (Kudielka, Broderick, & Kirschbaum, 2003). Participants were also asked to refrain from brushing their teeth and from consuming beverages containing caffeine or protein-rich meals up to an hour prior to sampling. The median duration of the interval between the preoperative resting day and the day of surgery was five days. The median duration of the interval between surgery and the postoperative resting day was 29 days. If samples had not been returned one month after discharge a letter of reminder was sent.

7.3.3 Measures

Cortisol analyses Salivary cortisol is considered to be a reliable and valid measure of the biologically active cortisol, as correlations between salivary and plasma-free cortisol are high (Kirschbaum & Hellhammer, 1989). Saliva was collected into purpose-designed Salivette tubes (Saarstedt, Chur, Switzerland). These tubes contain a cotton swab which is to be chewed for one minute and then returned into the vial. After collecting a diurnal profile, samples were temporarily stored in a home-based or hospital fridge. After retrieval by the study personnel, samples were frozen at -24°C. After thawing, samples were centrifuged at 3,000 g for two minutes. Vials containing less than 0.1 ml of saliva were discarded. Salivary cortisol concentrations were determined using a luminometric immuno-absorbent assay (IBL, Hamburg, Germany). Samples were processed according to the specifications of the assay manufacturer on a Tecan Genesis RSP 150 robotic sample processor (Tecan, Mannedorf, Switzerland) and on the Fluoroskan Ascent FL Luminometer (Labsystems, Kuopio, Finland). Interassay and intra-assay coefficients of variation (CV) were determined from samples as well as standards provided by the assay manufacturer. Mean interassay CV was 4.4% and mean intra-assay CV was 5.6% with none of the intra-assay CV across the study exceeding 10%.

Psychometric measures *Trait anxiety* was measured with the German version of the 20-item subscale of the State-Trait Anxiety Inventory (Laux, Glanzmann, Schaffner, & Spielberger, 1981). Psychometric properties are reported to be moderate or good. For the present data we observed a Cronbach's alpha of 0.94. *Anxiety and depressive mood* were assessed by the 14-item German version of the Hospital Anxiety and Depression Scale (Herrmann, Buss, & Snaith, 1994). This self-report measure consists of the anxiety (HADS-A) and the depressive mood (HADS-D) subscales. Good psychometric performance indices have been reported. Here we observed a Cronbach's alpha of 0.84 and 0.82, respectively. Suggestions regarding cut-off values exist to categorise scores within a range of 0-7 as clinically non-relevant, 8-10 as borderline, and 11-21 as clinically relevant. *Health-related quality of life* was assessed by the German version of the SF-36 health survey using the acute version (Bullinger & Kirchberger, 1998). The SF-36 provides for the calculation of eight subscales, a physical (KSK) and a mental health summary score (PSK) with a mean value of 50 (sd=10). The lower the summary score, the lower is the perception of subjective health functioning. In the reference sample, the short form of the SF-36, the SF-12, was used. During development of the SF-12, it was shown that the mental and physical health summary scores of the SF-12 explain more than 80% of the variance in the corresponding SF-36 summary scales (Ware, Kosinski, & Keller, 1996). Both versions are psychometrically robust and valid instruments for the assessment of subjective health functioning (Gandek et al., 1998). Finally, *subjective stress perception* was indicated on a 5-point Likert scale (1 = no distress; 2 = feelings of some distress; 3 = feelings of considerable distress; 4 = feelings of strong distress; 5 = extremely distressed).

7.3.4 Statistical Analyses

Frequency distributions for sociodemographic data and psychological measures were compared between the study and the reference sample. Group comparisons for continual data were performed by means of analyses of variances. In the case of distorted distribution of data or inhomogeneous variances, the non-parametric Wilcoxon signed-rank test was applied. Categorical data were compared by means of the Chi-square test.

To elucidate the variation in cortisol levels, we used multilevel-modelling, a variant of the multiple linear regression model. These models appropriately account for the hierarchical structure of the data with samples being nested within days and the days being nested within individuals. We refer to the three levels as the sample level, day level, and person level. In contrast to repeated measures analysis within the General

Linear Model approach, hierarchical linear models have the additional advantage of allowing for varying numbers of assessments per person. Furthermore, observations do not need to be equally spaced over time. As dependent variable, we used the natural log transformation of the raw cortisol values, which yielded a normal distribution. With regard to the independent variables, continuous data were centered around their mean.

The aforementioned hypothesis regarding differences in cortisol secretion between study and reference sample was tested in the following fashion as documented in table 7.2: First, the Null Model was derived to estimate the variance in the transformed cortisol values without any underlying assumption as to their composition. Next we modelled on estimates for the diurnal rhythm by introducing a dummy variable for the awakening sample, a slope term for the diurnal decline (Model 1) (Hruschka, Kohrt, & Worthman, 2005), as well as a second-order polynomial to allow for a non-linear trend in the diurnal decline (Model 2). Next we checked whether permitting random variation of the intercept and the diurnal slope at the person level and the day level considerably improved the model fit. This reflects our assumption about between- as well as within-person variability in diurnal cortisol secretion (Model 3-4). Additionally, we allowed for random variation for the squared diurnal slope term at the person level (Model 5). Subsequently, to test for differences in cortisol levels between study sample and reference group, we entered dummy variables for the pre-, peri-, and postoperative day, and the working day of the reference sample. The resting day of the reference sample served as the reference category (Model 6). We chose the resting rather than the working day as the reference category, since the study sample had collected pre- and postoperative saliva on a resting day. This is an important consideration as cortisol levels, particularly those after awakening, on working days and weekends have been shown to differ (Kunz-Ebrecht, Kirschbaum, Marmot, & Steptoe, 2004). To address differences in diurnal decline we further introduced interaction terms between the dummy variables encoding the type of day and diurnal slope (Model 7). Next, we explored possible differences regarding the awakening cortisol value by introducing interaction terms between the type of day and the dummy for awakening cortisol (Model 8). Finally, to control for group differences, we added a dummy variable for sex with females serving as the reference category, and the variables education and occupational qualification. Age and depressive mood were also entered into the model (Model 9). The interpretation of the interaction terms, e.g., awakening sample on the day of surgery, was rendered difficult as one cannot simply consider the β-coefficient of the interaction term. Instead the awakening sample on the day of surgery must be interpreted as a function of the intercept, the overall awakening cortisol prediction and the day by awakening sample interaction term. To facilitate interpretation we calculated an independent model (Model 9a) in

Table 7.2: Iterative development of the multilevel model to test for group differences in cortisol secretion (hypothesis 1).

	Modell description	Exploration of random structures			-2*log	delta -2*log	Δ df	p for Δ delta -2*log
		sample-level	day-level	person-level				
Null Model	Intercept	intercept	-	-	6740			
Model 1	add: dummy for awakening cortisol; diurnal slope	intercept	-	-	4752	1988	2	< 0.001
Model 2	add: 2nd order polynomial for diurnal slope	intercept	-	-	4699	53	1	< 0.001
Model 3	as above	intercept	intercept	intercept	4343	356	2	< 0.001
Model 4	as above	intercept	intercept diurnal slope	intercept diurnal slope	4243	100	2	< 0.001
Model 5[1]	as above	intercept	intercept diurnal slope	intercept diurnal slope (diurnal slope)^2	4215	28	1	< 0.001
Model 6[1]	add: dummies for type of day (reference: resting day of reference sample)	as above	as above	as above	4182	33	4	< 0.001
Model 7[1]	add: interaction terms between type of day and diurnal slope	as above	as above	as above	4160	22	4	< 0.001
Model 8[1]	add: interaction terms between type of day and awakening sample	as above	as above	as above	4144	16	4	0.002
Model 9[1]	add: control variables: dummy for male participants, age, depressive mood, education, occupational qualification	as above	as above	as above	4138	6	5	0.306

[1] estimates presented in table 7.5

Table 7.3: Iterative development of a multilevel model to test for effects of the day of surgery and psychological characteristics (hypotheses 2, 3a and 3b).

	Modell description	Exploration of random structures			-2*log	delta -2*log	Δdf	p for Δdelta -2*log
		sample-level	day-level	person-level				
Null Model	Intercept	intercept	-	-	2200			
Model 1	add: dummy for awakening cortisol; diurnal slope	intercept	-	-	1433	767	2	< 0.001
Model 2	add: 2nd order polynomial for diurnal slope	intercept	-	-	1410	23	1	< 0.001
Model 3	as above	intercept	intercept	intercept	1331	79	2	< 0.001
Model 4[1]	as above	intercept	intercept diurnal slope	intercept diurnal slope	1303	28	2	< 0.001
Model 4a	as above	intercept	intercept diurnal slope	intercept diurnal slope (diurnal slope)2	1302	1	1	0.317
Model 5[1]	add: dummies for type of day (reference: preoperative day)	as above	as above	as above	1281	21	2	< 0.001
Model 6[1]	add: extracorporeal circuit time, dummies for surgical risk (reference: risk score = 1)	as above	as above	as above	1269	12	3	0.007
Model 7[1]	add: trait anxiety, depressive mood, subjective stress perception	as above	as above	as above	1235	34	3	< 0.001

[1] estimates presented in table 7.6

which the interaction terms arising from Model 9 were coded as independent dummy variables.

To test the second hypothesis regarding diurnal cortisol secretion on the day of surgery, we applied a similar approach to the one used in the data analysis above. This iterative procedure is summarised in table 7.3. The first four steps involved decomposing the variance in cortisol values into its diurnal components (Model 1-2) and exploring the random structures for the model components at the day and person levels (Model 3-4). Next, dummy variables encoding the type of day were introduced. Here the preoperative day served as reference category (Model 5). To test the hypothesis regarding the effects of perioperative events and psychological variables, we extended Model 5 by adding variables encoding the severity of the surgical approach: the duration of extracorporeal circuit time in minutes and dummy variables encoding the surgical risk score of two and three. The lowest risk score (1) served as the reference category (Model 6). Finally, the psychological variables trait anxiety, depressive mood, and subjective stress perception were entered into the model (Model 7).

For all models the contribution of additional variables towards explaining the variance in the cortisol data was tested by comparing the previous fit with the fit of the subsequent model (delta -2*log) using Chi-square statistics (p for change delta -2*log). The fit statistics are presented in table 7.2 and 7.3, respectively. Further, to evaluate the contribution of single variables the unstandardised β-coefficients were extracted and tested by means of the Chi-square distribution.

The multilevel model estimates were calculated using MLwiN 2.02 software (Rasbash et al., 2000). For data management and further statistical analyses we used the software packages SAS 8.2 (SAS, Inc., Cary, NC) and SPSS 11.0 (SPSS, Chicago, IL). A probability level of $p<0.05$ was considered to indicate statistical significance across all statistical tests.

7.4 Results

7.4.1 Study sample

The group comparison between the study sample and the reference sample revealed compatibility for age, marital status, the number of children, and self-reported measures of physical and mental health as shown in table 7.4. Both groups reported good subjective health-related quality of life as indicated by the physical and mental health summary scores. However, groups differed with regard to their gender distribution, level of education and their occupational qualifications. The study sample comprised a

Table 7.4: Group differences between the study sample and the reference sample.

Sample characteristics	Study sample (n=57)	Reference sample (n=77)	
Demographics			
Males (%)	27 (47.4)	70 (91.0)	**
Age in years, mean (sd)	37.6 (6.4)	38.7 (4.9)	
Marital status, with partner (%)	56 (98)	75 (97)	
Number of children, mean (sd)	1.8 (0.8)	1.9 (0.8)	
Education			*
Secondary school (%)	2 (4)	3 (4)	
Upper secondary school (%)	21 (37)	50 (65)	
University entrance diploma (%)	34 (59)	24 (31)	
Occupational qualification			*
Without (%)	0 (0)	2 (3)	
Vocational training (%)	1 (2)	0 (0)	
Apprenticeship (%)	4 (7)	22 (29)	
Technical college (%)	23 (40)	37 (48)	
Applied science (%)	19 (33)	10 (13)	
University (%)	10 (18)	6 (8)	
Physical and mental health			
KSK, mean (sd)	52.0 (5.6)	52.3 (8.0)	
PSK, mean (sd	48.7 (12.2)	47.4 (9.9)	
HADS - A, mean (sd)	7.1 (4.0)	6.9 (2.7)	
HADS - D, mean (sd)	3.6 (5.6)	4.0 (5.4)	

** group differences with p <0.001; * group differences with p <0.001

higher women-to-men ratio, and participants had a higher education as well as higher occupational qualifications than those in the reference sample.

7.4.2 Overall cortisol secretion before, during and after the day of surgery

Table 7.5 presents estimates for selected preliminary models and the final model, which controls for the observed group differences in baseline characteristics. As expected, most of the variance in cortisol secretion was explained by modelling the circadian rhythm. Contrasting cortisol levels of the study sample with cortisol levels on a resting day from the reference sample revealed higher overall levels of cortisol for parents of children with CHD on the day of surgery, as evidenced by significant day variables for parents of children undergoing heart surgery (β=0.46, p<0.001). This translates into an overall increase of 36% over the levels on a resting day for working parents. Levels were marginally elevated on the postoperative day when the observed sociodemographic differences between groups were adjusted for (β=0.21, p=0.057). No significant differences in cortisol levels were observed between the resting day before surgery and the resting day of the reference sample after controlling for group differences. Modelling of the awakening levels as separate dummy variables (Model 9a) revealed similar awakening levels across all days in parents with children undergoing surgery, but lower awakening levels in the reference sample on a working and a resting day when compared with the estimate for the intercept (see Table 7.6). As awakening levels in parents did not differ from the intercept, this implies somewhat higher awakening levels in the study sample than in the reference sample. The significantly steeper diurnal declines on the preoperative and the postoperative days imply that cortisol levels returned more rapidly to lower levels in parents with children undergoing surgery, except for the actual day of surgery. Figure 7.1 illustrates the estimates of the circadian curve derived from Model 9a while simultaneously considering all variables in the model.

7.4.3 Cortisol secretion on the day of surgery

Table 7.7 provides estimates regarding the relationship between surgery-related data, psychological variables and cortisol secretion on the day of surgery (Model 7). We observed that a longer duration of extracorporeal circuit time related to higher levels in cortisol on the day of surgery. However, the effects were relatively small as indicated by β=0.06 per hour machine time. With regard to the surgical risk for the child, parents whose children were subjected to a surgical risk of two (β=-0.24, p<0.01) or three (β=-0.24, p<0.01) showed significantly lower overall levels of cortisol than those with the lowest risk. Neither trait anxiety nor depressive mood were associated with levels of

Table 7.5: Multilevel estimates for group differences in cortisol secretion between the study and the reference sample.

	Model 5			Model 6			Model 7			Model 8			Model 9		
N=2328	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p
Intercept	3.043	0.037	***	2.922	0.052	***	2.914	0.055	***	2.870	0.060	***	2.785	0.254	***
awakening cortisol	-0.434	0.037	***	-0.434	0.037	***	-0.428	0.037	***	-0.296	0.079	***	-0.296	0.079	***
diurnal decline (linear)	-0.242	0.012	***	-0.242	0.012	***	-0.236	0.013	***	-0.232	0.014	***	-0.232	0.014	***
diurnal decline (squared)	0.005	0.001	***	0.005	0.001	***	0.005	0.001	***	0.005	0.001	***	0.005	0.001	***
preoperative day				0.122	0.074	0.097	0.196	0.081	*	0.186	0.091	*	0.162	0.103	0.115
day of surgery				0.437	0.078	***	0.402	0.086	***	0.485	0.097	***	0.461	0.108	***
postoperative day				0.175	0.078	*	0.266	0.086	**	0.238	0.097	*	0.209	0.110	0.057
working day (reference sample)				0.081	0.045	0.072	0.052	0.051	0.309	0.136	0.060	*	0.135	0.060	*
preoperative day x diurnal slope							-0.026	0.011	*	-0.026	0.012	*	-0.026	0.012	*
day of surgery x diurnal slope							0.006	0.011	0.611	-0.003	0.012	0.780	-0.003	0.012	0.780
postoperative day x diurnal slope							-0.031	0.012	**	-0.029	0.013	*	-0.029	0.013	*
working day x diurnal slope (reference sample)							0.008	0.007	0.228	0.001	0.008	0.953	0.001	0.008	0.888
preoperative day x awakening cortisol										0.038	0.126	0.764	0.036	0.126	0.772
day of surgery x awakening cortisol										-0.246	0.135	0.068	-0.246	0.135	0.067
postoperative day x awakening cortisol										0.085	0.134	0.525	0.085	0.134	0.525
working day x awakening cortisol										-0.240	0.090	**	-0.239	0.090	**
sex (males)													-0.089	0.071	0.209
age													0.004	0.004	0.378
depressive mood													0.005	0.008	0.571
education													0.057	0.061	0.350
occupation													-0.050	0.032	0.113

*** < 0.001; ** < 0.01; * < 0.05

Null Modell: $\beta = 1.944$ (SE = 0.021)

Table 7.6: Multilevel estimates for group differences in awakening cortisol secretion between the study and the reference sample.

	Model 9a		
N=2328	Estimate	SE	p
Intercept	2.790	0.256	***
diurnal decline (linear)	-0.232	0.013	***
diurnal decline (squared)	0.005	0.001	***
preoperative day	0.157	0.108	0.144
day of surgery	0.461	0.114	***
postoperative day	0.198	0.116	0.087
working day (reference sample)	0.134	0.065	*
awakening cortisol before surgery[1]	-0.099	0.124	0.424
awakening cortisol on the day of surgery[1]	-0.086	0.131	0.511
awakening cortisol after discharge[1]	-0.011	0.132	0.933
awakening cortisol on a working day (reference sample)[1]	-0.403	0.072	***
awakening cortisol on a resting day (reference sample)[1]	-0.299	0.081	***
sex (males)	-0.093	0.072	0.192
age	0.004	0.005	0.374
depressive mood	0.005	0.008	0.590
education	0.056	0.061	0.354
occupation	-0.050	0.032	0.114

*** < 0.001; ** < 0.01; * < 0.05

[1] based on comparison with the estimation of the intercept

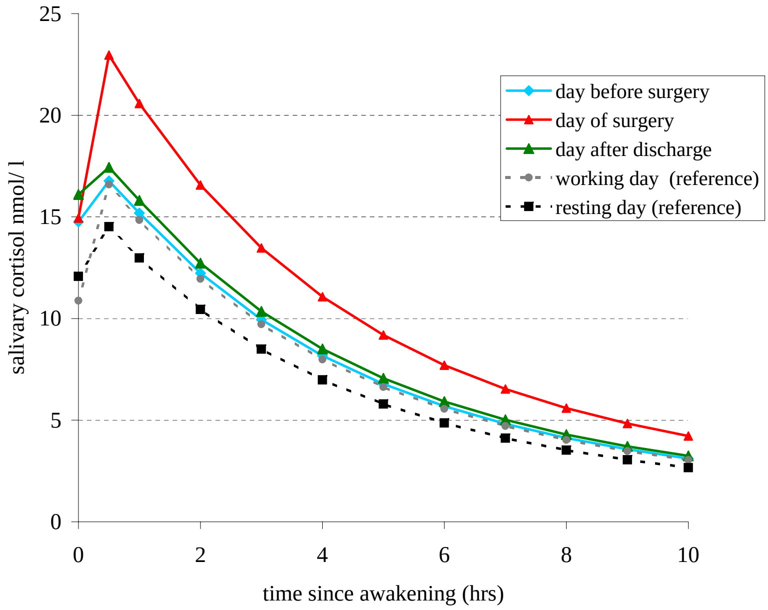

Figure 7.1: Group differences between the study sample and the reference sample.

cortisol. However, the subjective level of stress perceived at sampling showed a highly significant association with cortisol levels (β=0.11, p<0.001) and explained most of the difference between the preoperative day and the day of surgery.

7.5 Discussion

Little is known about circadian cortisol secretion in healthy adults exposed to prolonged or chronic stress. Elucidating the effects of prolonged stress on cortisol secretion may shed light on whether HPA activity is indeed involved in mediating the frequently observed association between chronic stress and physical disorders as well as psychopathology. In addition, assessing cortisol secretion in parents of children with CHD undergoing open-heart surgery allows for the evaluation of the effecst that surgery-related experiences may have on HPA activity particularly in these parents. While heightened levels of anxiety have been described for this population (Utens et al., 2000), nothing is known about the endocrine regulation before, during and after surgery on their child.

Consistent with our hypothesis, parents of children with CHD undergoing open-heart surgery showed higher overall levels of cortisol on the day of the child's operation than the reference group on a resting day. Moreover, the group comparison revealed marginally

Table 7.7: Multilevel estimates to test for the relationship of cortisol secretion with perioperative events and psychological characteristics .

	Model 5			Model 6			Model 7		
N=746	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p
Intercept	3.057	0.061	***	3.264	0.088	***	3.080	0.100	***
awakening cortisol	-0.336	0.062	***	-0.336	0.062	***	-0.332	0.061	***
diurnal decline (linear)	-0.254	0.017	***	-0.254	0.017	***	-0.255	0.017	***
diurnal decline (squared)	0.005	0.001	***	0.005	0.001	***	0.005	0.001	***
day of surgery[1]	0.314	0.066	***	0.322	0.066	***	0.177	0.075	*
postoperative day[1]	0.024	0.066	0.719	0.024	0.066	0.713	0.039	0.066	0.557
extracorporeal circuit time				0.059	0.025	*	0.058	0.024	*
surgical risk score 2				-0.250	0.092	**	-0.242	0.093	**
surgical risk score 3				-0.220	0.086	**	-0.239	0.089	**
trait anxiety							-0.002	0.004	0.688
depressive mood							0.010	0.011	0.359
subjective stress							0.111	0.029	***

Null Modell: $\beta = 1.944$ (SE = 0.021)
*** < 0.001; ** < 0.01; * < 0.05; 1 reference - day before surgery

elevated levels in the affected parents after their child had been discharged from hospital. However, we did not observe significant alterations in cortisol secretion for the resting day before surgery in parents of children with CHD. The overall elevation in levels of cortisol on the day of surgery is in line with the observations by Friedman and colleagues, who reported considerable increases in urinary 17-hydroxycorticosteroid under intense levels of psychological distress in parents of children with cancer (Friedman et al., 1963). Our study approach expanded on these findings by comparing data from the study sample with a reference sample comprising working parents with healthy children. Thus, we found cortisol levels in parents before surgery of their child comparable to levels in parents of healthy children. This may imply that the mere anticipation of the surgical event, which is associated with fear, uncertainty, and a great degree of psychological distress (Wray & Sensky, 2004), did not alter overall HPA activity in parents a few days before surgery. At most, the differences were as large as the differences between a working day and a resting day in parents of children without CHD, as visible in the graphical display of the estimates. Here the circadian curves for parents on a day before surgery and those for parents of healthy children on a working day adhere to similar levels throughout the day, except for the morning cortisol levels. However, while the diurnal cortisol secretion in the reference sample on a working day significantly differed from the cortisol secretion on a resting day, this did not show in the statistical testing for cortisol levels in the study sample on a preoperative resting day. The smaller sample size of the latter group may have reduced the statistical power. This assumption is supported by the fact that in contrast to the final model, preliminary multilevel models with fewer predictors indicated significantly higher levels in cortisol on a resting day for parents before surgery of their child.

With regard to cortisol secretion in parents after discharge of their child from hospital, we found elevated levels compared to a resting day in the reference sample. The observed group difference just missed the pre-defined level of statistical significance in the final model. Again, considering the small sample size and the high number of predictors in the final model, we cautiously interpret this as a trend towards elevation in overall cortisol secretion on the resting day after discharge. With reservation, the increased overall HPA activity in parents may result from the experiences related to surgery and hospitalisation, with the associated disruption of daily routines including sleeping and eating habits, and the worries the parents faced after their child had been discharged from hospital. Such findings would be in line with observed overall cortisol secretion in other stress-exposed caregiving populations, for instance in spouses of demented patients (Da Roza Davis & Cowen, 2001; Bauer et al., 2000; Vedhara et al., 1999).

Besides the overall cortisol secretion we also considered specific diurnal components on the pre-, peri- and postoperative day, including cortisol levels immediately after awakening, the morning rise, and the diurnal decline in cortisol secretion. Parents of children undergoing open-heart surgery showed higher cortisol levels immediately after awakening across all days compared to parents of healthy children. The diurnal decline in cortisol secretion both on the preoperative and the postoperative day was somewhat steeper than the decline in the reference sample. Thus, prolonged stress in parents of children undergoing open-heart surgery predominantly affected cortisol levels in the morning, while levels returned to normal in the evening. In contrast to studies that demonstrated positive associations between the morning rise and perceived chronic stress imposed by job strain (Steptoe et al., 2000), work overload (Schulz et al., 1998), social stress and worry (Wust et al., 2000), or non-specific everyday-life events in the healthy adult population (Pruessner et al., 1999), the parents in this study only showed a marked rise in morning cortisol when experiencing acute psychological distress, i.e. on the day of surgery. This may suggest that heightened cortisol levels upon awakening impose a limit as to how high morning levels in cortisol levels can possibly rise when exposed to prolonged stress. It takes an extremely distressing event, such as open-heart surgery in one's child, to observe a marked rise in morning cortisol on top of elevated cortisol awakening levels. The marked increase after awakening on the day of surgery may have occurred in anticipation of the forthcoming operation. As the morning rise has frequently been found to be particularly sensitive to stress-related phenomena, this has lead to speculations about its physiological meaning. For instance, it has been postulated that the morning rise plays a role in mediating the relationship between psychosocial variables and health-related issues (Clow et al., 2004). From an evolutionary perspective, this marked shift in circadian cortisol secretion prior to surgery may be viewed as a physiological mechanism preparing parents for a situation in which danger may require greater energy expenditure and immunocompetence to facilitate protection of their offspring.

Lastly, we explored whether surgery-related events and person-specific characteristics were associated with cortisol secretion in parents. The duration of the cardiopulmonary bypass procedure was related to higher mean values in cortisol. The machine time is indicative of the overall duration of the surgical procedures. Thus, parents who waited longer for the surgical procedures to end showed increased HPA activity for a longer period of time, explaining the slight increase in mean cortisol levels across the whole day. To our surprise, parents with an operative risk score of two or three displayed considerably lower mean cortisol values than parents whose children had a surgical risk score of only one, after simultaneously controlling for the duration of bypass time. This observation contrasts with the idea that there is a positive relationship between perceived threat and HPA activity as one might expect that parents who know about the higher risk for their child have higher perioperative cortisol secretion.

Considering psychological characteristics, cortisol secretion was not explained by preoperative levels of trait anxiety or depressive mood. This contrasts with previous findings in the literature, which described a relationship between affect and HPA regulation (Polk, Cohen, Doyle, Skoner, & Kirschbaum, 2005; Zobel et al., 2004). However, although our sample displayed normally distributed levels of anxiety and depressive mood, the sample was biased towards levels of anxiety and depression of little or no clinical relevance. Subclinical levels of anxiety and depressive mood may not suffice to induce the known alterations in HPA activity. In contrast, the subjective perception of distress during the day of surgery explained a large proportion of the cortisol increase on that day. This suggests that the appraisal of the situation as stressful or threatening was the most powerful modulator of the circadian cortisol secretion pattern.

Strength and limitations of the study

To our knowledge, this is the first prospective field study examining diurnal HPA activity with enduring levels of intense psychological distress on top of prolonged stress exposure in healthy middle-aged participants. The availability of reference data enabled us not only to contrast preoperative HPA activity with peri- and postoperative activity, but also to evaluate the extent to which diurnal cortisol secretion in parents of children with CHD is generally different from that in other parents. The elaborate multilevel approach to the data analysis allowed for consideration of all participants, despite some missing cortisol samples. Missing data is a general problem in field studies, yet investigating participants during a psychologically distressing event, such as the day of open-heart surgery, makes it particularly difficult to obtain complete data sets.

Nevertheless, several limitations of the study must be acknowledged. Ethical considerations led us to recruit only those parents who were emotionally stable enough to meet the additional demands of the study protocol and whose children had a low to medium operative risk score. Hence results cannot be generalised to the whole population of parents of children with CHD. We speculate, however, that the observed effects would be even more pronounced in the whole parent population. Another limitation results from the selected reference group. As selection was constrained by means of availability, we were unable to compare the study sample with parents from the same socioeconomic background and with the same distribution of gender. To amend for this limitation, we controlled for group differences statistically. Even so, there may be features inherent in the dissimilar group characteristics that were not captured by our control variables.

To sum up, the current study demonstrated that prolonged stress possibly causes an elevation of overall cortisol levels, comparable to the difference between a resting and a working day usually seen in the working population. Chronic stress may be particularly reflected in awakening cortisol levels, rather than in a marked morning rise. Effects however, are estimated to be small and it is yet to be determined whether they are of any clinical significance. Extreme levels of psychological stress on top of a prolonged stress experience cause a tonic shift in HPA activity characterised by a higher cortisol level upon awakening, a steeper morning rise after awakening and an overall elevation in cortisol secretion during the day until evening hours. Furthermore, while HPA activity appears to be very sensitive to the objective characteristics of an acute stressor, such as duration and threat, as well as the subjective perception of this stressor, the associated changes are rather small, implying a relatively rigid scale of hormonal adjustment beyond the known cortisol bursts in response to an acute stressor. The finding that most of the elevation in cortisol secretion patterns can statistically be explained by the subjective stress perception at sampling suggests that exploring avenues of psychosocial intervention and of monitoring stress levels may be beneficial, without having to resort to physiological measurements.

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8 Prediction of posttraumatic stress symptoms in parents after open-heart surgery in their child - A prospective cohort study

8.1 Abstract

Aims: Retrospective studies have shown that parents of children with a life-threatening illness are at an increased risk of suffering from symptoms of posttraumatic stress disorder. There is a scarcity of data evaluating risk factors prior to an illness-related trauma. The present study aimed at determining risk factors for symptoms of acute posttraumatic stress in parents after open-heart surgery for congenital heart disease in their child by means of a prospective study design.
Methods: The Posttraumatic Stress Diagnostic Scale served to predict the severity of acute symptoms of posttraumatic stress in a cohort of 188 parents of 113 children after open-heart surgery from (1) pre-, peri- and postoperative data of the child; and (2) parental demographic characteristics. For a subset of these parents, additional predictors were available including (3) preoperatively assessed psychosocial characteristics; and (4) diurnal cortisol secretion before and on the day of surgery. Sociodemographic and surgery-related information was abstracted from the medical records. Parents completed standardised questionnaires on psychosocial characteristics prior to the child's admission to hospital and after discharge. Saliva samples were repeatedly collected on a resting day before surgery and on the day of surgery. Multiple linear regression was used to predict the severity of acute symptoms of posttraumatic stress one month after open-heart surgery.
Results: A total of 29.3% of the parents experienced a significant degree of acute symptoms of surgery-related posttraumatic stress approximately one month after open-heart surgery on their child. With regard to sociodemographic risk factors, female gender and low occupational qualifications predicted symptom severity. None of the pre-, peri-, and postoperative data of the child significantly explained the variance in acute posttraumatic stress symptoms in parents, except for the occurrence of postoperative complications. Controlling for levels of neuroticism, preoperative parental anxiety was a significant predictor of the severity of acute stress symptoms. Preoperative endocrine

activity, measured by means of the morning rise in cortisol, significantly related to levels of acute posttraumatic stress in the parents.
Conclusion: Parents of children with congenital heart disease undergoing open-heart surgery are at an increased risk of suffering from surgery-related acute posttraumatic stress. Current results suggest that, besides sociodemographic risk factors and post-operative complications in the child, there may be psychological as well as endocrine vulnerability to the development of more severe symptoms of posttraumatic stress.

8.2 Introduction

Medical advances in surgery and supportive care techniques, as well as the increasing aggressiveness of medical treatment regimens, have significantly reduced mortality in serious paediatric illness. This medical progress has generated a new population of parents facing challenging responsibilities, uncertainties and fears (Santacroce, 2003; Lawoko & Soares, 2002). Acquired or congenital childhood disorder has been shown to impose greater distress on parents and is associated with an increased risk of suffering from psychopathology for affected mothers and fathers (Davis, Brown, Bakeman, & Campbell, 1998; Wallander & Varni, 1998; Grootenhuis & Last, 1997; Brown et al., 1993). Posttraumatic stress disorder (PTSD) in particular has received research attention in studies evaluating the long-term consequences of caring for a child with a life-threatening illness (Kean, Kelsay, Wamboldt, & Wamboldt, 2006; Landolt, Vollrath, Laimbacher, Gnehm, & Sennhauser, 2005; Kazak et al., 2004; Young et al., 2003; Manne, Du Hamel, Gallelli, Sorgen, & Redd, 1998).

According to the DSM-IV (APA, 1994), formal diagnostic criteria must be met before PTSD can be diagnosed. The first criterion concerns the experience of actual or threatened death, serious injury, or a threat to the physical integrity of oneself or others involving intense levels of fear, helplessness or horror. The actual symptoms must comprise re-experiencing aspects of the trauma, avoidance of trauma-related stimuli and a numbing of affect, and symptoms of excessive arousal. Diagnostic time constraints are imposed as symptoms must have persisted for more than one month (acute PTSD) or for more than three months (chronic PTSD).

With regard to parents of paediatric patients, heightened levels of anxiety and helplessness have previously been demonstrated in relation to the vulnerable physical integrity of their child, imposed by the disease itself or associated treatments such as cardiac surgery in CHD (Utens et al., 2000). More than a third of all children with CHD require palliative or corrective surgery in early life, while others may need surgical correction during childhood or adolescence (Marino, Bird, & Wernovsky, 2001; Samanek, 2000).

The surgical correction of a child's heart potentially constitutes an extremely distressing event for the parents and is associated with uncertainties about the outcome, fears about risks and complications. Accordingly, heightened psychological distress and maladaptive coping have been observed in parents before cardiac surgery (Utens et al., 2000; Wray & Sensky, 2004). Postoperative hospitalisation in an intensive care unit may impose further traumatic stress, as parents are confronted with the intubated child, occasionally with open thorax, the unfamiliar ICU environment, and possibly with postoperative complications (Balluffi et al., 2004; Board & Ryan-Wenger, 2002).

The experience of a traumatic event, however, does not inevitably lead to the development of PTSD (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). This suggests the presence of risk factors determining the vulnerability of an individual to developing PTSD (Yehuda, 1999). Therefore, beyond estimating the rate of parents who experience significant levels of posttraumatic stress after open-heart surgery in their child, it is of major interest to identify factors that differentiate between those parents who will develop symptoms of posttraumatic stress and those who will not. The identification of risk factors will assist in tailoring interventions to parents who are at increased risk of suffering from surgery-related posttraumatic stress after surgery in their child.

Within the general PTSD research, several risk factors have been identified in victims of traumatisation (Ozer, Best, Lipsey, & Weiss, 2003; Brewin, Andrews, & Valentine, 2000). Among the consistently identified risk factors for the civilian population are the severity of the trauma itself, female gender, young age, low socioeconomic status, lack of education, and lack of social support (Brewin et al., 2000). Furthermore, personality traits have been observed that predict PTSD in fire-fighters (Heinrichs et al., 2005) or in civilians exposed to air raid attacks (Knezevic, Opacic, Savic, & Priebe, 2005). With regard to paediatric intensive care parents experiencing acute levels of traumatic stress during hospitalisation of their child were observed to be more likely to develop PTSD after discharge (Balluffi et al., 2004).

The idea of a biological predisposition to the development of PTSD has received inconsistent empirical support. Based on the notion of a hypersensitive hypothalamus-pituitary adrenal axis in chronic PTSD (Yehuda, 1998), attempts have been made to determine whether this alteration is a consequence of traumatisation or whether it precedes the development of PTSD. Some studies, which evaluated cortisol levels in victims during the immediate aftermath of a stressful event, found lowered cortisol secretion in those who went on to develop PTSD (Delahanty, Raimonde, & Spoonster, 2000). Previous traumatisation may have mediated this observation (Delahanty, Raimonde, Spoonster, & Cullado, 2003; Resnick, Yehuda, Pitman, & Foy, 1995). In contrast, McFarlane and colleagues did not observe any differences in initial levels of cortisol between victims of motor vehicle accidents with subsequent PTSD and those without symptoms of PTSD (McFarlane, Atchison, & Yehuda, 1997). Independent of the inconsistencies, these studies do not allow the evaluation of dispositional factors of PTSD but only of peritraumatic factors. As it is inherent in the nature of traumatic events that they occur unexpectedly, it is difficult to measure potential risk factors before the event occurs. One exception lies with high-risk populations, such as fire-fighters, who are prone to experiencing traumatic events during their job performance. A recent study by Heinrichs and colleagues assessed diurnal cortisol secretion in fire-fighters during training before fire service entry (Heinrichs et al., 2005). Initial levels of cortisol did not predict the development of PTSD at a two-year follow up. However, the scarcity of prospective data does not allow to draw final conclusions as to the vulnerability to PTSD in relation to the hypothalamus pituitary axis.

In sum, while research into the aetiology of PTSD has so far failed to consistently identify markers of a biological predisposition, some sociodemographic risk factors as well as aspects of personality have repeatedly been shown to differentiate between people who develop PTSD after a traumatic event and those who do not. It is unclear to what extent previous research findings may be applicable to parents of children with severe CHD undergoing open-heart surgery. The potentially traumatising event of open-heart surgery differs in many aspects from previously investigated traumatic events, such as war, rape, or road accidents. Firstly, the trauma does not threaten the physical integrity of the individual concerned but that of his or her child. Secondly, the event does not always occur unexpectedly, as in the case of elective surgery or prenatal diagnosis of the heart defect. Nevertheless, there is large scope for unexpectedness with regard to perioperative events and the postoperative course. Thirdly, the event involves a much larger time span as it includes a preparatory phase, the actual day of surgery, and the time it takes for the child to recover from surgery. Singular surgery-related events, as well as the entire experience, may have the potential to induce posttraumatic stress in the affected parents. However, despite enduring anxiety, worry and feelings of helplessness, the greatest difference from other traumatic events may arise from the hopes parents associate with the surgical events.

The current study aimed at evaluating the extent to which parents of children with CHD undergoing open-heart surgery experience acute symptoms of surgery-related posttraumatic stress after their child's discharge from hospital. Additionally, the predictive value of pre-, peri, and postoperative data of the child for the severity of parental stress symptoms was evaluated. Finally, with regard to preoperatively assessed parental characteristics, the predictive value of sociodemographic, psychosocial and endocrine data for posttraumatic symptom severity was explored.

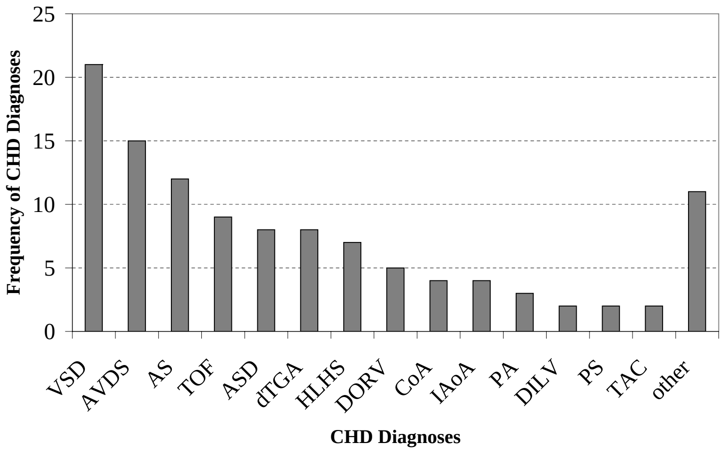

Figure 8.1: Distribution of CHD diagnoses with indications for open-heart surgery in children of participating parents. *Abbreviations: AS-aortic stenosis; ASD-atrial septal defect; AVSD-atrioventricle septum defect; CoA-coarctation of the aorta; DILV-double inlet left ventricle; DORV-double outlet right ventricle; dTGA-d-transposition of the great arteries; HLHS-hypoplastic left-heart syndrome; IaoA-interrupted aortic arch; PA-pulmonary atresia; PS-pulmonic stenosis; TAC-truncus arteriosus communis; TOF-tetralogy of Fallot; VSD-ventricle septal defect*

8.3 Methods

8.3.1 Participants and procedure

A total of 188 parents (41.5% males) of 113 children with CHD partook in the study after their child had been discharged from hospital following open-heart surgery between July 2004 and December 2005. Figure 8.1 gives an overview of the distribution of the CHD diagnoses in these children. Parents had a mean age of 36.4 years (sd = 6.3 years). Most of them were of Caucasian origin (95.7%), three parents were of African and one parent of Asian origin.

Fifty-nine percent of these parents (N = 110, 40.9% males) provided information on psychosocial characteristics before their child was admitted to hospital for surgery (mean age: 36.7 years, sd = 7.1 years). A further subgroup of 56 parents (47.4% males) provided salivary samples for cortisol analyses in addition to answering questionnaires prior to surgery and after discharge of their child (mean age: 37.8 years, sd = 6.4 years). In the following, parents who answered questionnaires only after surgery are referred to as Sample A. Parents who provided psychosocial information prior to and after surgery, including parents who collected saliva samples, comprise Sample B. The subgroup of parents who collected saliva in addition to pre- and postoperative psychosocial questionnaires are referred to as Sample C. Figure 8.2 summarises the different types of parental participation in this study.

Recruitment was run as follows: Two separate recruitment strategies were adopted due to the children's different surgery-related circumstances. The first strategy concerned parents with children undergoing elective open-heart surgery (Sample B). These parents were approached by the study coordinator several weeks prior to surgery and were provided with written information on the study. Parents who expressed interest received the standardised questionnaire including items on personality, anxiety, depressive mood, previous traumatisation, and social support. Parents were asked to return the questionnaire on the day of admission of their child. After their child had been successfully operated on and was ready for discharge from the hospital, parents were given the follow-up questionnaire containing items on psychosocial outcome, e.g., surgery-related posttraumatic stress. Questionnaires were taken home and returned in a prepaid envelope. If a questionnaire had not been returned four weeks after discharge a reminder letter was sent. Some parents felt unable to answer questions relating to their emotional and psychological state before surgery of their child. These parents were included in the follow-up assessment only. The latter approach was also adopted for parents who had experienced emergency open-heart surgery in their child, typically in newborns with CHD. In the face of ethical constraints and time constrictions these parents were approached after successful surgery of their child. One inclusion criterion for all recruitment strategies was a sufficient command of the German language. With regard to the cortisol measures, parents were only approached if their child was to undergo elective open-heart surgery with a low to medium surgical risk score. The particular criteria for inclusion or exclusion from the cortisol protocol are described in Chapter 7.3.1. Parents were required to collect saliva samples on a typical resting day prior to surgery, on the day of surgery, and on a typical resting day after their child's discharge from hospital. Samples were taken immediately after awakening, 30 minutes after awakening, at 8.30 a.m., 11.30 a.m., 4 p.m., and 8 p.m. The procedure is described in detail in Chapter 7.3.2.

All parents provided informed consent. No incentive was offered except for information about the study results. The study was approved by the Ethics Committee of the Children's Hospital of the University Zurich.

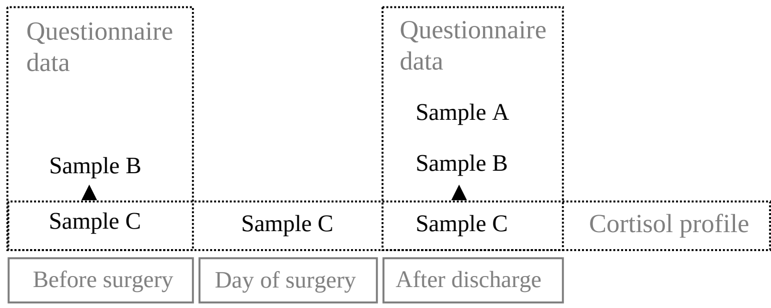

Figure 8.2: Schematic overview of different types of parental study participation with regard to Samples A, B, C

8.3.2 Psychological measures

Outcome assessment at follow up: To assess surgery-related posttraumatic stress in parents after discharge of their child from hospital the Posttraumatic Diagnostic Scale (PDS) was used (Foa, Cashman, Jaycox, & Perry, 1997). The PDS is a widely used screening instrument to assess PTSD in clinical and research settings according to DSM-IV criteria (APA, 1994). Here we used the German version (Steil & Ehlers, 2000). Three subscales rate self-reported symptoms of re-experiencing (5 items), avoidance (7 items), and excessive arousal (5 items) according to the frequency of their occurrence. PTSD is diagnosed if at least one symptom of re-experiencing, three symptoms of avoidance, and two arousal symptoms are present at least one month after the trauma. Symptom frequency is assessed on a 4-point Likert scale (from "not at all" to "almost always"). The PDS has been recommended for use with continual measures serving as an index of symptom severity (Foa et al., 1997). As we were interested in evaluating surgery-related posttraumatic stress the general word "trauma" was substituted with the word "heart surgery" in the instructions of the questionnaire. Internal consistencies with values for Cronbach's alpha between 0.73 and 0.79 were observed for the subscales with the current data.

Levels of pre- and postoperative anxiety and depressive mood were assessed using the Hospital Anxiety and Depression Inventory (Zigmond & Snaith, 1983) in its German version (Herrmann, Buss, & Snaith, 1994). This self-report measure consists of the anxiety subscale (HADS-A) and the depressive mood subscale (HADS-D), each comprising seven items which are rated on a 4-point Likert scale. Good psychometric performance indices have been reported. We observed values for Cronbach's alpha of 0.83 and 0.86, respectively. Suggestions regarding cut-off values exist, categorising scores on each scale within a range of 0-7 as clinically non-relevant, 8-10 as borderline, and 11-21 as clinically relevant levels of anxiety or depressive mood.

Prospective assessment of psychosocial predictors: Prior to surgery a proportion of parents filled in a questionnaire, which included measures of psychosocial characteristics including the HADS. Neuroticism was measured with the neuroticism subscale of the NEO Five Factor Inventory (Costa & McCrae, 1989) in its German version (Borkenau & Ostendorf, 1993). The scale consists of 12 items assessing emotional stability and lability in an individual on a 5-point Likert scale. High levels of neuroticism imply more negative emotions and a greater degree of worrying. The internal consistency of the scale was good as indicated by the value for Cronbach's alpha of 0.85.

Social support was assessed with the short version of the FsozU-K-14, a German instrument for the assessment of social support (Fydrich, Sommer, & Brähler, 2002). Internal consistency was high.

The relationship of the participants with their partner was evaluated with the communality-communication and the conflict subscales of the German Relationship Questionnaire (Hahlweg, 1996), a widely used instrument in psychotherapy settings and clinical research. The communality-communication scale consists of 10 items, which assess the degree of shared activities and aspects of communication in a relationship. A high score indicates a positive bond between partners. The 10 items of the conflict subscale measure behavioural patterns in the partner during conflict, as perceived by the respondent. High scores indicate less advantageous behaviour in the partner. The internal consistencies of both scales were high with values for Cronbach's alpha of 0.97 and 0.96, respectively.

Life events of the past twelve months, excluding surgery-related events, were assessed by the Life Event Scale, a checklist of twelve life events such as pregnancy, moving house, or unemployment (Landolt et al., 2002).

Finally, to check for previous traumatisation, a trauma anamnesis was conducted. Participants were presented with a list of eleven traumatic life events including natural disaster, severe accidents, physical assault, or rape (Steil & Ehlers, 2000). If at least one event on the list had previously been experienced, the PDS questionnaire, as described above, was answered to allow screening for pre-existing symptoms of PTSD.

The order of the scales included was randomly distributed across participants to avoid systematic error due to serial effects.

8.3.3 Medical data

Medical data regarding the pre-, peri-, and postoperative course of all children operated on during the study period were extracted from medical records by the study coordinator, providing the parents had given permission. Preoperative medical data concerned aspects such as previous open-heart surgery, presence of cyanosis, heart insufficiency, or known genetic defects. Perioperative data relating to the surgical risk according to the RACHS-1 risk stratification (Jenkins et al., 2002), to the duration of extracorporeal circuitry and the application of surgical support methods, e.g. deep hypothermia, were extracted. Data indicative of the postoperative course were, for instance, postoperative complications, duration of mechanical ventilation, length of stay in the intensive care unit and overall hospitalisation. Additionally, sociodemographic data were extracted.

8.3.4 Cortisol analyses

Salivary cortisol is considered to be a reliable and valid measure of the biologically active cortisol, as correlations between salivary and plasma free cortisol have been demonstrated to be high (Kirschbaum & Hellhammer, 1989). Saliva was collected into purpose- designed Salivette tubes (Saarstedt, Chur, Switzerland) for later analyses of unbound and biologically active cortisol. These tubes contain a cotton swab, which is chewed for one minute and then returned to the vial. After collecting a diurnal profile, samples were temporarily stored in a home-based or hospital fridge. After retrieval by the study personnel, samples were frozen at -20°C. After thawing, samples were centrifuged at 3,000 g for two minutes. Vials containing less than 0.1 ml of saliva were discarded. Salivary cortisol concentrations were determined using a luminometric immuno-absorbent assay (IBL, Hamburg, Germany). Samples were processed according to the specifications of the assay manufacturer on a Tecan Genesis RSP 150 robotic sample processor (Tecan, Mannedorf, Switzerland) and on the Fluoroskan Ascent FL Luminometer (Labsystems, Kuopio, Finland). Interassay and intra-assay coefficients of variation (CV) were determined from samples as well as from standards provided by the assay manufacturer. Mean interassay CV was 4.4% and mean intra-assay CV was 5.6% with none of the intra-assay CV across the study exceeding 10%.

8.3.5 Statistical Analyses

To estimate the representativeness of all participating parents with regard to sociodemographic situation and their child's medical status, we compared data for children whose parents had participated in the study (Samples A and B) with data for children whose parents had declined to participate, yet had given permission for the scientific use of the medical records of their child. Out of all the parents whose children who underwent open-heart surgery during the study period, parents were only considered as potentially eligible if the mother had a fluent command of the German language. Non-parametric tests were applied to compare respondent with non-respondent continual data (e.g. Mann-Whitney) and ratio data (e.g. Chi-Square likelihood ratio). Similarly, differences between parents who provided psychosocial information before and after surgery on their child (Sample B) and those who participated in the study only after surgery (Sample A) were analysed using parametric or non-parametric statistical tests. Finally, we evaluated differences between parents who had collected salivary samples and had provided psychosocial information before and after surgery (Sample C) with parents who had participated only in the psychosocial part of study before and after surgery.

To estimate the level of acute posttraumatic stress in parents after discharge of their child from hospital, we calculated the sum of the symptom clusters for re-experience, avoidance, and excessive arousal of the PDS, which yielded a significantly skewed distribution of data towards the non-pathological end of the scale ($p = 0.005$). Thus, to enable further analysis without violating the assumption of a normally distributed independent variable we applied square root transformation to the PDS scores.

Next, the predictive quality of sociodemographic, pre-, peri- and postoperative variables for acute symptoms of posttraumatic stress in parents was pre-assessed by means of bivariate correlations for continual data and linear regression for dichotomous (e.g. presence or absence of cyanosis in the child) or nominal data (e.g. genetic defects) using dummy variables. To avoid effects of suppression and multicollinearity, only variables significantly related to symptom severity and not highly correlated among themselves were selected for the final analyses. Subsequently, the selected predictors were entered into a stepwise multiple linear regression model. The time interval that had elapsed between the day of surgery and the day parents had answered the questionnaire was forced into the model to adjust for the large heterogeneity in the postoperative interval. Three participants were removed from the final analysis (one male, two females) due to incomplete medical data of their child, making the sample size 185 participants.

With regard to the analysis of psychosocial predictors the statistical procedures were similar to the procedures described above. At first, bivariate correlations between the psychosocial variables and acute symptoms of posttraumatic stress were evaluated. Variables, which significantly related to stress symptoms, were included in the final stepwise multiple linear regression model. The control variables "postoperative interval" and "neuroticism" were forced into the model. We chose to control for neuroticism, which has frequently been associated with PTSD (Casella & Motta, 1990; Lewin, Carr, & Webster, 1998), as we presumed that there is a considerable degree of content overlap with the symptoms of arousal in neuroticism and PTSD (Engelhard, Hout, & Kindt, 2003). Seven participants (two males, five females) met diagnostic criteria for PTSD before surgery of their child according to the DSM-IV (APA, 1994). They were excluded from the analyses. One male participant was removed because of incomplete questionnaire data. This left a final sample of 102 participants in Sample B for the regression analysis.

Finally, to assess the predictive relationship between diurnal cortisol secretion on a pre- and postoperative resting day as well as on the day of surgery, raw cortisol values were transformed using the natural logarithm to obtain normally distributed data. The morning rise for each day and each individual was calculated as the difference between cortisol levels 30 minutes after awakening and cortisol levels immediately after awakening. In order to estimate the overall cortisol secretion after the morning peak, we calculated the area under the curve (AUC) using the trapezoid formula (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003) aggregating cortisol values from 90 minutes after awakening until 8pm. Parents who had not provided information on posttraumatic stress after discharge were excluded from further analyses ($n = 9$). Incomplete diurnal sampling on certain days meant that we only allowed analysis of participants who provided a sample upon awakening and at least three samples during the course of the day. The subsequent procedure followed the steps described above. First, the predictive relationship between measures of cortisol secretion and stress symptom severity was evaluated by means of bivariate correlations. Variables significantly correlating with posttraumatic stress were entered into the final stepwise multiple regression model adjusting for the time that had elapsed since surgery.

A p-value of <0.05 was considered to indicate statistical significance. For data management and statistical analyses we used the software packages SAS 8.2 (SAS, Inc., Cary, NC) and SPSS 11.0 (SPSS, Chicago, IL).

8.4 Results

8.4.1 Description of the samples

A total of 179 children with a German-speaking mother had undergone open-heart surgery during the study period. For 125 of those children at least one parent participated in the study (total $n = 188$ parents), which amounts to a response rate of 69.5% with regard to the children operated on. Comparing the child's data from respondents and non-respondents revealed comparability of the level of education and occupational qualification of mothers and fathers, the proportion of children with a genetic defect or with pre-operative heart insufficiency, the mean surgical risk score, the need for perioperative circulatory arrest, length of stay in the intensive care unit, the rate of postoperative complications, and overall duration of hospitalisation. Differences between participating parents and non-responding parents, were the older age of participating mothers ($p = 0.002$) and their children ($p = 0.038$), and, for children of participating parents, a higher level of mean oxygen saturation before surgery ($p = 0.013$), as well as a smaller likelihood of needing a stomach tube ($p = 0.020$) and of receiving deep hypothermia during heart surgery ($p = 0.032$). Considering the similar rates of complications, lengths of stay in the intensive care unit and hospitalization, these data indicate that children of participating parents had similar or slightly less severe CHD than children of non-participating parents.

Furthermore, differences between parents who had participated in the study before and after surgery and parents who had participated only after surgery were evaluated (Sample B vs. Sample A). Results are summarised in table 8.1. Comparability was observed for sociodemographic data. With regard to the medical status of the child, significant group differences generally implied that parents who had not participated in the study before surgery had younger children, and more severely ill children who were more often subjected to high-risk support methods. Also, children of parents in sample A took longer to recover from surgery than children of parents in Sample B. This reflects our approach of recruiting parents differently depending on the medical status of their child and the type of surgery (elective vs. emergency). Furthermore, after surgery, Sample A presented with higher mean levels of anxiety, depressive mood, and symptoms of posttraumatic stress.

Table 8.1 also presents differences between parents who had collected salivary samples (Sample C) and parent who had provided psychosocial information before and after surgery but no cortisol samples. Parents who provided cortisol data had higher occupational qualifications. None of their children was intubated before surgery and the children's age at surgery was higher. The postoperative course of the child was generally less difficult as indicated by the shorter length of stay in the intensive care unit and overall duration of hospitalisation. Levels of posttraumatic stress were lower compared to parents who did not provide cortisol data. The bias towards a sample of parents with less severely ill children reflects our recruitment strategy of including only less strained parents in the complex study protocol of collecting salivary samples and answering psychosocial questionnaires.

The retention rate for the follow up after discharge in parents who had participated in the study before surgery was 83.5%. One mother was not approached at follow up

Table 8.1: Group differences between samples A, B, and C.

	Variables	Types of parental particpiation Sample A (N= 84)	Sample B (N=101)	p[1]	Sample C (N=45)	p[2]
Sociodemographics						
	Gender (%males)	42.3	40.9		43.5	
	Age (mean, sd)	35.9 (5.0)	36.8 (7.1)		38.2 (6.7)	
	no. of children (mean, sd)	2.1 (1.3)	1.8 (0.8)		1.7 (0.7)	
	Education (% low)	6.4	3.6		4.3	
	Occupation (% low)	6.4	6.3		0.0	*
Medical history	Cyanosis (%)	40.0	26.4	*	21.9	
	Mean O_2 saturation (mean, sd)	91.0 (8.3)	93.2 (7.9)	*	93.9 (7.1)	
	Heart insufficiency (%)	14.6	9.1		8.7	
	Preoperative intubation (%)	9.3	0.9	**	0.0	*
	Genetic defect (%)	21.8	30.9		41.3	*
Perioperative data	Surgical age in years (mean, sd)	3.3 (4.6)	3.9 (5.2)	**	3.5 (4.3)	*
	Surgical risk score (mean, sd)	2.8 (0.1)	2.5 (0.8)		2.4 (0.7)	
	ECC duration in min (mean, sd)	156.0 (64.5)	145.0 (66.2)		148.9 (76.0)	
	Deep hypothermia (%)	20.0	5.5	**	8.7	
	Circulatory arrest (%)	8.0	1.8	*	4.3	
Postoperative data	Open thorax (%)	41.3	16.4	***	13.0	*
	Surgery-related complications (%)	46.2	42.7		50.0	
	Intubation in days (mean, sd)	3.5 (4.5)	2.4 (3.1)	*	2.0 (2.4)	
	Stay on ICU in days (mean, sd)	7.0 (6.9)	5.2 (5.0)	**	4.5 (3.6)	*
	Hospitalisation in days (mean, sd)	22.3 (17.7)	16.4 (11.7)	***	14.5 (9.8)	*
Postoperative psychological status	Anxiety (mean, sd)	5.7 (4.1)	4.4 (3.7)	*	4.7 (3.8)	
	Depressive mood (mean, sd)	4.6 (4.1)	3.1 (3.7)	*	3.0 (3.3)	
	PTS severity (mean, sd)	10.2 (2.0)	6.3 (2.0)	***	5.8 (2.0)	*

*** p<0.001; ** p<0.01; * p<0.05 (2-tailed)

[1] group comparison between Sample A (parents with postoperative psychosocial data only) and Sample B (parents with pre-and postoperative psychosocial data)

[2] group comparison between parents with pre-and postoperative psychosocial data (yet without cortisol, data not shown) and parents with pre-, postoperative psychosocial data and cortisol data (Sample C)

because her child died following surgery. The follow-up rate in parents who had collected saliva samples was 84.0%.

8.4.2 Evaluating the severity of acute surgery-related posttraumatic stress in parents after open-heart surgery in their child

A total of 55 out of the 188 participants (29.3%), 35 women (31.8%) and 20 (25.6%) men, experienced a significant degree of acute symptoms of posttraumatic stress, as they met the diagnostic criteria for the symptom clusters re-experiencing, avoidance, and excessive arousal on the PDS. The incidence rate for mothers with PTSD symptoms did not differ from the rate for fathers ($p = 0.40$). The mean postoperative interval amounted to 33 days (sd = 20.5, median = 27 days).

8.4.3 Predicting severity of posttraumatic stress symptoms from sociodemographic characteristics, pre-, peri-, and postoperative data

Table 8.2 provides an overview of the sociodemographic variables, and the pre-, peri-, and postoperative data for which we tested the relationship with posttraumatic stress in parents after discharge of their child. Based on the coefficient estimates and p-values eight variables were selected for further analyses. These comprised: female gender, low occupational qualifications, Trisomy 21 in the child, open thorax after surgery, haemodialysis in the child, postoperative complications, the length of stay in the intensive care unit and the overall duration of hospitalisation. As the latter two variables were highly correlated ($r = 0.87$, $p < 0.01$), only duration of hospitalisation was entered into the final model. Performing stepwise multiple linear regression revealed a final model, which explained 9% of the observed variance in severity of posttraumatic stress (see table 8.3). Controlling for the postoperative interval the results revealed three significant predictors. Low occupational qualifications, the experience of surgery-related postoperative complications in a child, and being female predicted more severe symptoms of posttraumatic stress in parents.

These results led us to explore further, what types of surgery-related complications predict symptom severity in parents. Complications were grouped into heart-related complications other than cardiac dysrhythmias, e.g. mitral insufficiency and cardial ischemia (affected parents n = 17), cardiac dysrhythmias (n = 14), lung-related complications other than pulmonary hypertensive crisis, e.g. pneumothorax (n = 22), pulmonary hypertensive crisis (n = 10), multiple complications, i.e. more than two postoperative complications (n = 10), and miscellaneous complications (n = 11). These conditions were compared with parents whose children had recovered from surgery without signifi-

Table 8.2: Overview of variables tested for their association with PTS in parents after open-heart surgery in their child.

	variables	β[a]	r[b]
Sociodemographics			
(N=185)	age		
	gender **	0.179**	
	number of children		
	educational level		
	low		
	intermediate		
	high		
	occupational qualification		
	low **	0.179**	
	intermediate		
	high		
Medical history of the child)			
(N=185)	prenatal diagnosis of CHD		
	previous open-heart surgery		
	cyanosis		
	heart insufficiency		
	genetic defect		
	Trisomy 21*	-0.124*	
	Microdeletion 22q11		
	other		
	suspected defect		
	previous abort		
Perioperative data of the child			
(N=185)	surgical risk		
	extracorporeal circuit duration		
	low flow duration		
	deepest body temperature		
	deep hypothermia		
	circulatory arrest		
Postoperative data of the child			
(N=185)	open thorax*	0.125*	
	dialysis*	0.137*	
	complications**	0.176**	
	duration of intubation		
	length of stay in intensive care**		0.155**
	duration of hospitalisation**		0.171**
Psychosocial data of the parents			
(N=102)	preoperative anxiety**		0.362**
	preoperativ depressive mood**		0.305**
	social support*		-0.168*
	life events		
	partnership conflicts		
	partnership communication		
Salivary cortisol in parents			
(N=45)	before surgery: morning rise**		0.313**
	AUC $_{day}$		
	day of surgery: morning rise		
	AUC $_{day}$		
	after discharge: morning rise		
	AUC $_{day}$		

[a] standardised [b] Pearson correlation
** p<0.05; * p<0.10 (2-tailed)

cant clinical difficulty (n = 111). Stepwise multiple linear regression analysis was applied to predict posttraumatic stress as a function of the dummy encoded categories controlling for the duration of the postoperative interval. For none of these complications did severity of parental posttraumatic stress differ from the posttraumatic stress levels in parents of children without postoperative complications. However, there was a positive trend for parents with children who had suffered from pulmonary hypertensive crisis (Beta = 0.131, p = 0.074). Considering the small sample size of affected parents (n = 10), this may, nonetheless, indicate that pulmonary hypertensive crisis in children after open-heart surgery is particularly associated with higher posttraumatic stress levels in parents after discharge.

8.4.4 Predicting severity of posttraumatic stress symptoms from psychosocial characteristics

All psychosocial variables tested for their correlation with posttraumatic stress are summarised in table 8.2. Based on the coefficient estimates and p-values three variables were selected for further analyses, namely social support, preoperative anxiety and preoperative levels of depressive mood. The control variable postoperative interval and neuroticism, were forced to remain in the model. Results are shown in table 8.3. The final model predicted 14% of the observed variance in acute posttraumatic stress symptoms. Preoperative anxiety significantly predicted stress severity in parents after discharge of their child from hospital. Neither social support (Beta = -0.65, p = 0.516) nor preoperative depressive mood (Beta = 0.55, p = 0.682) significantly predicted PTS severity.

8.4.5 Predicting severity of posttraumatic stress symptoms from diurnal salivary cortisol secretion

Table 8.2 also provides the estimated correlation coefficients between the morning rise in cortisol levels and the area under the curve with acute levels of posttraumatic stress. Only the morning rise on the resting day before surgery significantly related to symptoms of posttraumatic stress and was thus entered into the final regression model. Due to the limited sample size, and after controlling for the postoperative interval, the overall model failed to become significant (F = 2.48, df = 2/42, p = 0.096). However, the morning rise observed on the day before surgery remained significantly associated with the severity of acute posttraumatic stress in parents after discharge of their child (Beta = 0.332, p = 0.036). The time span of the morning rise ranged from 29 minutes to 45 minutes across parents for the sampling day before surgery. Therefore, we repeated the analysis for the estimated morning rise expected at 30 minutes. The observed morning rise was divided

Table 8.3: Stepwise multiple linear regression analysis of risk factors predictive of acute PTS symptom severity in parents one month after open-heart.

	Predictor	R^2	adjusted R^2	ΔR^2	ΔF	Δp	df	standardised Beta	t	p
Sample A (n=185)[a]	Postoperative intervall	0.002	-0.003	0.002	0.396	0.530	183	-0.002	-0.021	0.983
	Low occupational qualification (reference: high)	0.048	0.038	0.046	8.829	0.003	182	0.222	3.138	0.002
	Surgery-related complications (reference: none)	0.084	0.069	0.036	7.038	0.009	181	0.186	2.616	0.010
	Female gender (reference: males)	0.109	0.089	0.025	4.994	0.027	182	0.158	2.235	0.027
Sample B (n=101)[b]	Postoperative intervall							-0.063	-0.667	0.506
	Neuroticism	0.104	0.086	0.104	5.707	0.005	98	0.192	1.846	0.068
	Preoperative anxiety	0.168	0.142	0.063	7.397	0.008	97	0.287	2.720	0.008
Sample C (n=46)[c]	Postoperative intervall	0.001	-0.023	0.001	0.014	0.908	43	-0.087	-0.584	0.562
	Cortisol morning rise/ before surgery	0.106	0.063	0.105	4.940	0.032	42	0.332	2.223	0.036

[a] Model: F = 5.49; df = 4/ 180; p<0.001; [b] Model: F = 6.71; df = 3/ 98; p<0.001; [c] Model: F = 2.48; df = 2/ 42; p=0.096

by the difference between the exact time the sample taken 30 minutes after awakening and the exact time of the awakening sample, multiplied by 30 minutes. The adjusted morning rise retained a trend towards association with the square root of the symptom severity score (Beta = 0.271, p = 0.093).

8.5 Discussion

Caring for a child with a life-threatening illness, such as a CHD, has frequently been observed to cause elevated levels of parental distress or even symptoms of posttraumatic stress in affected mothers and fathers. The invasiveness of the procedure and the potentially high risk associated with open-heart surgery can be experienced as particularly threatening by the parents. Accordingly, the current study observed a significant degree of acute symptoms of posttraumatic stress in 29% of parents approximately one month after their child's surgery. Thus, 32% of the mothers and 26% of the fathers met diagnostic criteria for PTSD according to the DSM-IV (APA, 1994) with regard to re-experiencing surgery-related traumatic events, avoidance of trauma-related stimuli and numbing of affect, as well as excessive arousal. This observation compares to observed rates of current PTSD in parents of children with life-threatening asthma (Kean et al., 2006) and transplant recipients (Young et al., 2003) of 29% and 27%, respectively. Compared to the estimated life-time prevalence of PTSD in the normal population of 8% (Kessler et al., 1995) parents experiencing open-heart surgery in their child are clearly at an increased risk of suffering from significant levels of posttraumatic stress after surgery. Nevertheless, two thirds of the parents did not experience acute symptoms of PTSD after discharge of their child from hospital. Thus, we were interested in identifying factors that predicted symptom severity.

According to the general PTSD literature, the traumatic event itself, i.e., its severity, is a salient predictor of the development of PTSD (Brewin et al., 2000). We explored medical data indicative of the objective risks to the child imposed by surgical intervention. The preoperative status of the child, including the presence of cyanosis or heart insufficiency, did not relate to the severity of posttraumatic stress in parents. Neither were any of the perioperative variables associated with levels of parental posttraumatic stress. No differences in posttraumatic stress levels were observed between parents whose children underwent high-risk support methods, and parents of children who did not undergo deep hypothermia or circulatory arrest during surgery. In contrast, data indicative of the postoperative course in the child, such as the length of stay in the intensive care ward, overall hospitalisation and the occurrence of surgery-related postoperative complications in the child, were significantly associated with the severity of posttraumatic stress symptoms in parents. Controlling for the interval that had elapsed between surgery and the assessment of parental stress symptoms, the occurrence of postoperative complications continued to predict levels of posttraumatic stress. Besides the overall effect of postoperative complications, evaluation of subcategories revealed that parents of children who suffered from pulmonary hypertensive crisis were at particular risk of experiencing posttraumatic stress. Pulmonary hypertensive crisis is a severe and potentially life-threatening complication after cardiac surgery, necessitating extensive medical intervention.

In sum considering pre-, peri- and postoperative data of children undergoing open-heart surgery we demonstrated that neither the preoperative status of the child nor perioperative events predict acute symptoms of posttraumatic stress in the affected parents. In contrast the postoperative course appears to play a significant role. The relevance of postoperative complications may be explained by the parents' enduring fears and close witnessing of surgery-related events which occur on top of the event of open-heart surgery.

With regard to sociodemographic data we observed that mothers experienced more severe levels of acute posttraumatic stress than fathers. Although, at first sight, this is in line with the consistently documented higher vulnerability of women to PTSD (Brewin et al., 2000), comparison of the rates for mothers and fathers who met the diagnostic criteria for symptoms of PTSD did not reveal a gender difference. While mothers may be more prone to admit to full-scale emotional disturbance caused by the surgery, fathers may be more reluctant to do so. These findings emphasise the need to include mothers and fathers into studies assessing the impact of the child's illness on the family, just as well as the need to consider mothers and fathers equally when offering professional support to the parents before, during and after hospitalisation of their child. Moreover, we observed a higher risk in parents with low occupational qualifications than in parents with high job qualifications. This replicates observations in other studies which have documented an increased risk of PTSD in people with low socioeconomic status. For the current context, the finding may be considered in the light of the comparably low financial resources available to these parents. The hospitalisation of a child can induce an additional financial burden as unplanned costs for travelling and accommodation arise.

The assessment of parental states and traits, as well as environmental characteristics prior to surgery on their child, enabled the prospective analysis of the relationship between psychosocial variables and the development of posttraumatic stress after discharge from hospital. Adjusting for the postoperative interval and levels of neuroticism, preoperative anxiety remained the only relevant predictor. Psychological adjustment as implied by levels of anxiety or depressive mood prior to a trauma has repeatedly been observed to relate to the development of PTSD (Ozer et al., 2003). Yet most of these studies applied a retrospective design, which may have distorted findings due to the potential recall bias in PTSD associated with symptoms of avoidance, dissociation and amnesia. The current prospective data suggest, nonetheless, that some parents may have a psychological predisposition to developing surgery-related posttraumatic stress, characterised by heightened levels of preoperative anxiety. On the other hand, the elevation in levels of preoperative anxiety may only in part stem from a personality trait, it may also in be influenced by the forthcoming event of the heart surgery (Utens et al., 2000). The social environment of the parents, characterised by levels of social support and the quality of the relationship with the partner, did not predict levels of posttraumatic stress. Although the protective value of social support has consistently been described in the general PTSD literature (Brewin et al., 2000), it may not exert its protecting effect on parents during the hospitalisation of their child and the time immediately after the child's discharge.

Finally, besides a psychological vulnerability there may also be a biological predisposition to PTSD. To our knowledge, this is the first study demonstrating a positive relationship between endocrine activity before the traumatic event and the level of severity of acute posttraumatic stress. Nevertheless, the predictive value of the morning rise in levels of salivary cortisol in parents on a resting day before surgery must be considered with caution. Since the precise time of sampling cannot be exactly controlled in a field study, we adjusted the time interval between the awakening sample and the second sample taken approximately 30 minutes after awakening for the final analyses. Subsequently controlling for the postoperative interval, the cortisol morning rise no longer significantly predicted levels of surgery-related posttraumatic stress in parents, yet a statistical trend was still observed. In the face of the relatively low statistical power, we still hold with the assumption that there is a predictive relationship. In contrast, the overall cortisol secretion on any day did not relate to the severity of posttraumatic stress. This supports the idea that the morning rise and the remaining diurnal cortisol secretion are distinct physiological functions (Clow, Thorn, Evans, & Hucklebridge, 2004). Furthermore, this finding supports results that have demonstrated the particular sensitivity of the morning rise to stress-related phenomena (Wust, Federenko, Hellhammer, & Kirschbaum, 2000; Schulz, Kirschbaum, & Prässner, 1998).

In sum, the prospective analyses of person-specific characteristics in the current study point to several risk factors for the development of severe levels of acute posttraumatic stress in parents of children undergoing open-heart surgery. In line with the general PTSD literature, being female, having low job qualifications, and experiencing increased anxiety prior to the trauma predicted the severity of symptoms of posttraumatic stress.

In addition, the characteristic morning rise in salivary cortisol levels on a resting day before surgery was found to relate to later levels of posttraumatic stress.

Study limitations and implications

In view of the study results, several limitations must be acknowledged. The findings can only be generalised with caution to the whole population of parents of children with CHD undergoing open-heart surgery. Despite our thorough analyses of differences between non-respondents and respondents, as well as between the different samples (A, B, C), which allow an estimate of the degree of bias with respect to major predictive variables, the different recruitment strategies may have enforced a systematic bias on the entire sample, i.e., due to the fact that parents were approached prior to surgery only if their child was to undergo elective surgery. Thus, we cannot infer that there is a predictive relationship between preoperative psychological adjustment and PTSD severity in parents who experienced emergency surgery on their child or who were unable to answer psychosocial questionnaires prior to surgery. The same holds true for the conclusion regarding the relationship between preoperative cortisol secretion and levels of posttraumatic stress. The comparisons between groups with different patterns of participation indicated that parents of less severely ill children, and of children who took less time to recover from surgery, participated to a greater degree in the study. Consequently, a systematic bias contributing to an underestimation of the effects on surgery-related posttraumatic stress may underlie our observations. Another limitation lies in the heterogeneity of the time that elapsed between surgery and the assessment of posttraumatic stress levels in parents, which was mainly caused by variability in the postoperative course of recovery of the children. As one of the diagnostic criteria for PTSD requires that the symptoms persist for at least one month, we were unable to consider PTSD for the entire cohort, as some parents had provided the information within less than four weeks of surgery.

From the latter limitation the first implication arises, namely, that there should be a future follow up to observe who will meet diagnostic criteria of PTSD longitudinally after surgery in their child. The literature has shown that although acute symptoms of posttraumatic stress are a risk factor for developing PTSD (Bryant, Harvey, Guthrie, & Moulds, 2000), symptoms may also be transient and show acute remission (Blanchard et al., 1997). Further, future research may reassess the impact of the identified risk factors for severity of acute posttraumatic stress in the development of acute and chronic PTSD. Finally, besides research implications a wide range of consequences arise from these observations for application to the clinical context. These consequences may include the systematic psychosocial support of parents at risk of developing severe surgery-related posttraumatic stress before surgery, during hospitalisation and after discharge of their child. Also, with regard to biological determinants, first attempts have been made to introduce the pharmacological prevention of PTSD (Schelling, Roozendaal, & De Quervain, 2004). In any case, efforts should be made to assist affected parents in their psychological adjustment, not only because successful coping is important for the immediate recovery of the child but also for the child's long-term development (Visconti, Saudino, Rappaport, Newburger, & Bellinger, 2002).

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9 General discussion

9.1 Long-term adjustment in children with CHD after open-heart surgery: the parents‘ view

The systematic review of the literature regarding psychological adjustment and QoL in children with CHD after open-heart surgery (Chapter 4) revealed that parents, in particular, perceive signs of psychological maladjustment, i.e. significant behavioural difficulties, in these children. Furthermore, the existing literature supports the hypothesis that parental distress predicts the severity of later behavioural difficulties in children with CHD (Visconti, Saudino, Rappaport, Newburger, & Bellinger, 2002). The observed divergence between children's self-reports and parental perceptions may be explained by denial processes in the child and/or by maladaptive coping with the child's illness on the part of the parents. Independent of the reason why parents are more likely to perceive behavioural difficulties in their child than the children themselves, the review has highlighted the role parents may play in the psychological adjustment of children with CHD undergoing open-heart surgery.

Parents of children with CHD face various challenges as they need to adapt to the child's diagnosis (Tak & McCubbin, 2002), cope with illness-related concerns, such as the medical prognosis and financial issues (Horn, DeMaso, Gonzalez-Heydrich, & Erickson, 2001), as well as the experience of parenting stress caused by difficult child behaviour (Uzark & Jones, 2003) or high-risk surgical interventions (Utens et al., 2000). These threats to their psychosocial integrity may exhaust the resources of individual parents, possibly leading to symptoms of posttraumatic distress. Thus, the empirical part of this work was concerned with investigating how the event of open-heart surgery in a child affects parents in a physiological, as well as in a psychological, sense.

9.2 Diurnal cortisol secretion in parents of children with CHD

The hormone cortisol has frequently been used as an objective physiological marker of mental stress in experimental settings (Kudielka, Hellhammer, & Kirschbaum, in press) as well as in field studies (Hjortskov, Garde, Orbaek, & Hansen, 2004). To date, only few studies have assessed cortisol secretion in parents of children with a life-threatening illness (Glover & Poland, 2002; Friedman, Mason, & Hamburg, 1963). To our knowledge, there is a lack of studies regarding the diurnal secretion pattern in parents of children undergoing open-heart surgery. Thus, it is not known to what extent the anticipation of surgery, the experience of the actual day of surgery, and the overall hospitalisation of the child, including the potential surgery-related complications, are reflected in alterations in the HPA system. The current study tested hypotheses regarding a general elevation in levels of salivary cortisol in parents of children undergoing open-heart surgery.

The observed findings are not straightforward, yet they need to be considered in the light of the small sample size and the difficulty in obtaining a representative sample of parents undergoing this sort of extreme emotional stress. Firstly, ethical considerations led to the definition of very strict inclusion criteria requiring emotional stability in the parents and a relatively low surgical risk for the child. Secondly, despite fulfilling the inclusion criteria many parents declined to collect saliva for the study purpose for personal reasons. Thus, the included sample possibly comprises a group of relatively stress-resistant and emotionally stable parents. In these parents cortisol levels were particularly high on the day of surgery. In the face of the extremely distressing event this finding is not surprising. In contrast, the effects on parental cortisol secretion on the resting days before and after the child's surgery were less pronounced, but nevertheless to some degree evident. Findings imply that on a resting day parents of children with CHD show cortisol levels comparable to levels otherwise secreted on a working day. Weekday-weekend differences in cortisol secretion have repeatedly been observed in the working population, particularly for morning cortisol (Kunz-Ebrecht, Kirschbaum, Marmot, & Steptoe, 2004). Indeed across all days cortisol levels immediately after awakening were significantly higher in parents with children undergoing surgery than in the reference sample. The observations may indicate that anticipation of surgery as well as the surgery-related experiences have an enduring effect on the HPA axis in affected parents, characterised by increased cortisol secretion upon awakening and slightly elevated levels during the day. Levels do not appear to return to normal once the child has been discharged from hospital. Nevertheless, the observed effects were relatively small and their clinical relevance remains unclear. With regard to the selection bias of the sample it is assumed, however, that effects may be underestimated as parents who were emotionally overwhelmed by the situation and/or whose children were undergoing surgery with a very high risk were not admitted to this part of the study.

Several implications arise from these observations. As an enduring elevation of cortisol levels can exert immunosuppressive effects, it would be of interest to ascertain whether parents of children with CHD experience more physical symptoms or a higher morbidity than parents of healthy children. More importantly, the potential causes of the elevation in cortisol levels, particularly after the discharge of the child from hospital, needs to be considered, in order to take steps to alleviate the stress in parents. Although surgery may have successfully been completed and the child is recovering, there are many aspects that might cause prolonged stress in this population. While there was medical support available 24 hours a day during hospitalisation, most parents are left to themselves after discharge and have to manage the special needs of their child without any professional assistance at home. Besides the actual parental responsibilities, there may be fears about a sudden deterioration in the child's condition. Various support strategies may assist parents in this difficult situation. For instance, it may be helpful to provide information and planning assistance to parents during hospitalisation so that they know what to expect at home with regard to the child's progress, as well as their own well being. Parents should be reassured that it is perfectly normal to feel physically and emotionally exhausted after the experiences in hospital and that they should allow themselves to rest. This may, however, be hampered by the demanding task of caring for the child, possibly also for the child's siblings, or by other work-related responsibilities.

Another observation of the study demonstrated the importance of subjective stress perception on cortisol secretion. The differences between cortisol levels on resting days and those on the day of surgery were explained to a great extent by the subjective stress perception in the respective situation. This may demonstrate the scope for supportive interventions. While the situation, i.e. the need for surgery, cannot be changed, the subjective perception of the situation may be more prone to modification. Many approaches are conceivable, yet they may depend on the resources of the respective hospital and the affected parents themselves. From the clinical side, provision of regular information on the progress of surgery and psychosocial or spiritual care upon request may affect distress perception.

In sum, it has been demonstrated that the event of open-heart surgery in one's child has the potential to induce lasting alterations in HPA activity in healthy middle-aged parents. This may have various implications for the support of these parents during the acute phase of the child's treatment and immediately after his or her discharge from hospital. While the cortisol analyses served to evaluate the effect of prolonged stress on parents caused by the event of surgery, the assessment of levels of posttraumatic stress aimed at elucidating the extent to which open-heart surgery in one's child may also qualify as a traumatising event with lasting effects on the psychological adjustment of parents.

9.3 Posttraumatic stress symptoms in parents of children with CHD

One of the most striking findings of this work is the fact that almost one third of the parents of children with CHD experienced a significant degree of acute symptoms of surgery-related PTSD (see Chapter 8). One can only speculate about how many of the parents who did not partake in the study also suffered from acute posttraumatic stress after the discharge of their child. As the avoidance of trauma-related stimuli is a prominent symptom of PTSD, it is possible that symptoms were particularly present in the non-respondent parents as they no longer wished to deal with surgery-related questioning. Out of the 179 children operated on during the study period, we received responses for 125 children from at least one parent. A total of 188 parents provided information on their psychological well-being after their child's discharge. Presuming that most of the children lived with mother and father in their families illustrates that the response rate was just above 50% across all parents of children undergoing surgery. Thus, our observations regarding the incidence rate of acute surgery-related PTSD in parents may underestimate the true number of affected parents. Furthermore, a positive bias towards a better psychological outcome in parents may have resulted from the implementation of the study itself. For instance, the content of study information and questionnaires may have altered cognitions and increased awareness in participating parents, thus changing their coping strategies and psychological adjustment. The availability of an additional contact person, i.e. the study coordinator, may have served as a non-specific, but to some extent effective, intervention. Taking these considerations together, it is emphasised that at least one third of all parents of children undergoing open-heart surgery experience acute symptoms of surgery-related posttraumatic stress. The response bias in participation, as well as the intervening character of the study, may have contributed to an underestimation of the true effect of surgery-related experiences on the affected parent population.

The observed incidence rate for significant surgery-related posttraumatic stress in parents of children with CHD in this study compares to prevalence rates for PTSD previously reported for parents of childhood cancer survivors. Depending on the time of assessment, prevalence rates ranged from 10% (Kazak et al., 1997) to 40% (Stuber, Christakis, Houskamp, & Kazak, 1996). However, while it has been established that paediatric oncological centres in Germany must offer continual psychosocial support to families of children undergoing oncological treatment, no such regulation exists for the context of paediatric cardiology and cardiosurgery. Instead psychosocial services for families of children with heart defects are generally not consulted until symptoms of psychological decompensation become evident. The current study's results highlight the need for professional support for families of children with CHD before surgery and during hospitalisation to prevent, rather than to treat, symptoms of psychopathology.

The observations of surgery-related posttraumatic stress were extended by the analyses of the potential risk factors for heightened stress levels. As a result, the following risk factors were identified. These may indicate who is in particular need of psychosocial support:

- postoperative complications in the child
- female gender (only with regard to severity but not to occurrence of posttraumatic stress)
- a low job qualification
- higher preoperative levels of anxiety in parents
- (a higher morning rise in levels of cortisol in parents)

Speculations as to why these factors may have caused elevated levels of posttraumatic stress are beyond the scope of this work, since numerous factors relate to the postoperative course of the children, to the roles of mothers and fathers, to their individual job situation and to anxiety levels before surgery. As an example, preoperative anxiety may in some parents be the correlate of a personality trait, whereas in other parents it may simply reflect an emotional state, namely, one of justified fear before a high-risk surgical intervention.

Also, it is very difficult to deduce specific implications for systematic intervention without knowing the exact circumstances of the clinical context where surgery takes place, including personal ability, financial resources, and willingness towards change. Furthermore, to date there is a lack of empirical knowledge on both how to reduce anxiety in parents of children with CHD before surgery, and how to provide effective support for parents following surgery, for instance in the case of postoperative complications in a child. As a starting point, maladaptive coping strategies, such as social isolation and inertia, have been observed in parents before their child's cardiac surgery (Utens et al., 2000). Moreover, cognitive-behavioural interventions, such as problem-solving skill training, have been shown to effectively reduce negative affectivity in mothers of children with newly diagnosed cancer (Sahler et al., 2002). Based on these observations systematic interventions may be developed specifically for parents whose children need open-heart surgery. Finally, current empirical findings from the general PTSD literature evaluating psychotherapeutic intervention administered shortly after traumatisation are also encouraging in demonstrating the effectiveness of this treatment (Bryant, Sackville, Dang, Moulds, & Guthrie, 1999). Thus, early psychological intervention given to parents during and following hospitalisation of their child may help to prevent or reduce the risk of developing surgery-related PTSD in these parents.

Besides the development and the evaluation of effective interventions to prevent acute posttraumatic stress in parents of children undergoing open-heart surgery, future research needs to investigate the long-term course of surgery-related symptoms of PTSD in affected parents. It is not known whether the observed symptoms are transient and will show acute remission in affected parents, or who may be at particular risk to develop chronic PTSD. Reconsidering research assessing PTSD in parents of childhood cancer survivors, a substantial proportion of parents with chronic illness-related posttraumatic stress symptoms (Kazak et al., 2004) have been described. Moreover, parents of children admitted to a paediatric intensive care unit who experienced symptoms of acute traumatic stress, were more likely to develop PTSD months after their child's discharge from intensive care (Balluffi et al., 2004). The current study is based on an ongoing cohort study and parents will be reassessed with regard to their psychosocial well-being and their levels of surgery-related posttraumatic stress six and twelve months after their child's surgery.

9.4 Limitations of the study

Limitations with regard to the methodological approach have already been discussed in the respective empirical chapters, 7 and 8. In more general terms a few more considerations must be added. Although all parents who participated in the study had children with an inborn heart defect, and all of these children underwent open-heart surgery, there is great heterogeneity as to the individual situations relating to the medical prognosis for the child, the option for complete correction of the defect, their surgical history and comorbidities. By subsuming all of these children under the general term of CHD and assessing HPA activity and levels of posttraumatic stress in their parents, specific circumstances inherent in the individual diagnoses may have escaped appropriate attention.

Another thought concerns the use of standardised questionnaires within the context of this work. A few participating parents commented on the questionnaires during the study, stating that they do not fully cover their experiences. An alternative approach would, therefore, be to combine quantitative with qualitative data, or to design more context-specific questionnaires.

9.5 Last note

In response to the limited scope of standardised questionnaires, parents also had the opportunity to answer open questions about their individual surgery-related experiences. A selection of comments is presented in Appendix B. These utterances provide in-depth insights into their thoughts and experiences; their suggestions for change may also serve as a starting point for the development of future studies and interventions.

9.6 References

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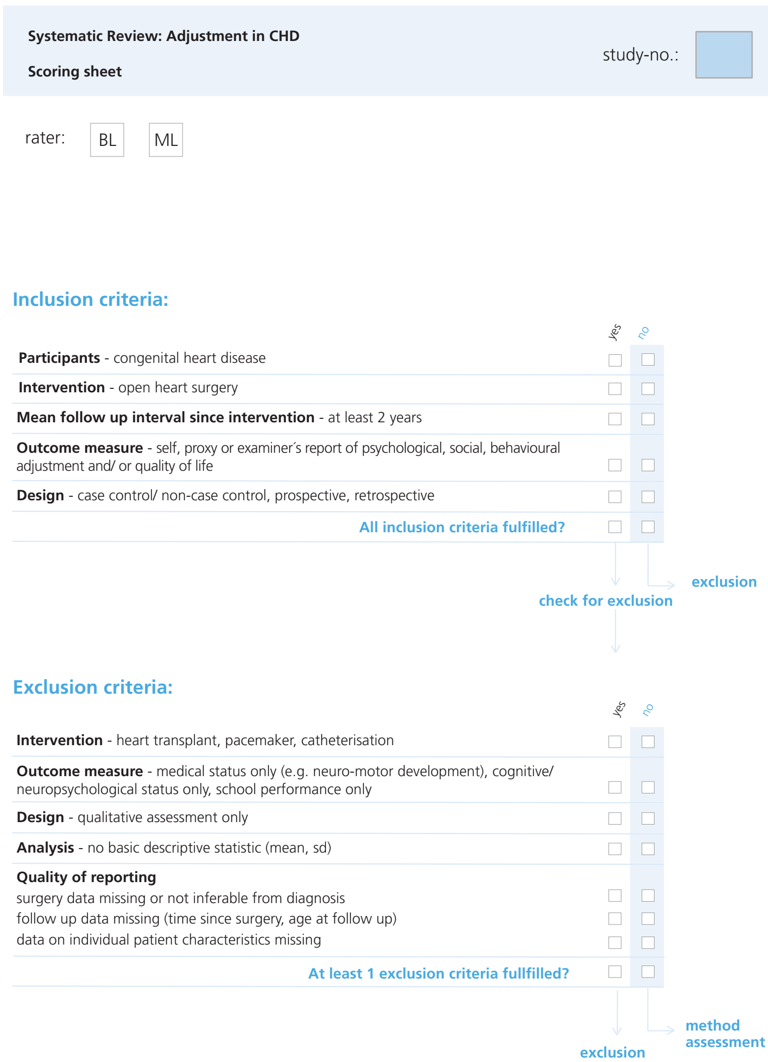
Appendix A

Systematic Review (Chapter 4)



Systematic Review: Adjustment in CHD

Scoring sheet

study-no.:

rater: BL ML

Inclusion criteria:

	yes	no
Participants - congenital heart disease	☐	☐
Intervention - open heart surgery	☐	☐
Mean follow up interval since intervention - at least 2 years	☐	☐
Outcome measure - self, proxy or examiner´s report of psychological, social, behavioural adjustment and/ or quality of life	☐	☐
Design - case control/ non-case control, prospective, retrospective	☐	☐
All inclusion criteria fulfilled?	☐	☐

exclusion

check for exclusion

Exclusion criteria:

	yes	no
Intervention - heart transplant, pacemaker, catheterisation	☐	☐
Outcome measure - medical status only (e.g. neuro-motor development), cognitive/ neuropsychological status only, school performance only	☐	☐
Design - qualitative assessment only	☐	☐
Analysis - no basic descriptive statistic (mean, sd)	☐	☐
Quality of reporting		
surgery data missing or not inferable from diagnosis	☐	☐
follow up data missing (time since surgery, age at follow up)	☐	☐
data on individual patient characteristics missing	☐	☐
At least 1 exclusion criteria fullfilled?	☐	☐

method assessment

exclusion

Figure A.1: Systematic review: Inclusion and exclusion criteria

Table A.1: Systematic review: Excluded studies

study	reason for exclusion
(Andersen, Horder, Kristensen, & Mickley, 1994)	pacemaker implantation
(Bauer et al., 2001)	heart transplants
(Bellinger, Bernstein, Kirkwood, Rappaport, & Newburger, 2003)	visuo-spatial outcome only
(Brandhagen, Feldt, & Williams, 1991)	mean age at follow up > 25 years
(Brousse et al., 2003)	50% of sample with acquired heart disease
(Casey, Sykes, Craig, Power, & Mulholland, 1996)	surgery data unclear
(Casey, Craig, & Mulholland, 1994)	< 50% OHS with HLM
(Chen, Li, & Wang, 2005)	< 50% OHS with HLM
(Chen, Li, & Wang, 2004)	< 50% OHS with HLM
(Connolly, McClowry, Hayman, Mahony, & Artman, 2004)	postoperative follow up < 2 years
(DeMaso et al., 1991)	surgery data unclear
(Di Filippo, Bozio, Sassolas, Champsaur, & Ninet, 1997)	heart transplants
(Dittrich, Bührer, Grimmer, Abdul-Khaliq, & Lange, 2003)	neurodevelopmental outcome only
(Drago et al., 1991)	no basic statistics
(Plessis et al., 2002)	neurological outcome
(Favarato & Romano, 1994)	publication in Portuguese
(Forbess et al., 2002)	neurodevelopmental outcome only
(Goldberg et al., 1997)	surgery data unclear
(Gomelsky, Holden, Ellerbeck, & Brenner, 1998)	neurodevelopmental outcome only
(Gupta, Mitchell, Giuffre, & Crawford, 2001)	< 50% OHS with HLM
(Haneda, Itoh, Togo, Ohmi, & Mohri, 1996)	cognitive outcome only
(Horner, Liberthson, & Jellinek, 2000)	mean age at follow up > 25 years
(Huang, Wang, & Chen, 1996)	publication in Chinese
(Immer, Althaus, Berdat, Saner, & Carrel, 2005)	mean age at follow up > 25 years
(Janus & Goldberg, 1995)	< 50% OHS with HLM
(Kaemmerer et al., 1994)	no basic statistics
(Kao, Wang, Pai, & Hwang, 2000)	publication in Chinese
(Kato et al., 1993)	cognitive outcome only
(Kirshbom et al., 2002)	cognitive outcome and health only
(Kokkonen & Paavilainen, 1992)	< 50% OHS with HLM
(Krol et al., 2003)	< 50% OHS with HLM
(Lane, Lip, & Millane, 2002)	mean age at follow up > 25 years
(LeBidois, Kachaner, Vouhe, Sidi, & Tamisier, 1992)	heart transplants
(Limperopoulos et al., 2001)	postoperative follow up < 2 years
(Miller, Tesman, Ramer, Baylen, & Myers, 1996)	neurodevelopmental outcome only
(Moons et al., 2004)	no basic statistics
(Moyen Laane et al., 1997)	surgery data unclear
(Newburger et al., 2003)	cognitive outcome only
(Puca, Marino, Covino, & Lombardi, 1996)	sample includes acquired heart disease
(Ratzmann, Schneider, & Richter, 1991)	postoperative follow up < 2 years
(Sharma et al., 2000)	neurodevelopmental outcome only
(Simko & McGinnis, 2003)	mean age at follow up > 25 years

Table A.1: continued

study	reason for exclusion
(Spurkland, Bjorbae, & Hagemo, 2001)	heart transplants
(Spurkland, Bjornstad, Lindberg, & Seem, 1993)	postoperative follow up $<$ 2 years
(Sticker, Schmidt, & Steins, 2003)	surgery data unclear
(Ternestedt et al., 2001)	mean age at follow up $>$ 25 years
(Wernovsky et al., 2000)	cognitive outcome only
(Williams, McCrindle, & Ashburn, 2003)	no basic statistics
(Wray & Maynard, 2005)	sample includes acquired heart disease
(Wray & Radley-Smith, 2004)	preoperative assessment only
(Wray & Sensky, 2001)	postoperative follow up $<$ 2 years
(Wray & Sensky, 1999)	postoperative follow up $<$ 2 years
(Wray & Sensky, 1998)	postoperative follow up $<$ 2 years
(Wray, Pot-Mees, Zeitlin, Radley-Smith, & Yacoub, 1994)	heart transplants
(Rijen et al., 2005)	mean age at follow up $>$ 25 years
(Rijen et al., 2005)	mean age at follow up $>$ 25 years
(Rijen et al., 2004)	mean age at follow up $>$ 25 years
(Rijen et al., 2003)	mean age at follow up $>$ 25 years
(Visconti, Bichell, Jonas, Newburger, & Bellinger, 1999)	neurodevelopmental outcome only
(Yang, Liu, & Townes, 1994)	preoperative assessment only
(Yildiz, Savaser, & Tatlioglu, 2001)	$<$ 50% OHS with HLM

dissertations	reason for exclusion
(Burgess, 2002)	health-related beliefs only
(Connor, 2003)	postoperative follow up $<$ 2 years
(Greenwood, 1999)	mean age at follow up $>$ 25 years
(Limperopoulos, 2002)	neurodevelopmental outcome only
(Mroz, 1992)	postoperative follow up $<$ 2 years
(Rosenberg, 1999)	mean age at follow up $>$ 25 years
(Simko, 2000)	mean age at follow up $>$ 25 years

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Assessment of method	3	2	1
1. Avoidance of selection bias	all patients from medical data base included or random selection from data base	selection bias possible due to criteria such as distance from setting, regular follow up appointments in clinic, compliance, motivation	selection method not reported; obvious selection bias, inferable confounding
2. Avoidance of non-response bias	85% or more response rate; in case of group design – no difference in response rate between groups	response rate between 85 – 65%; in case of group design – difference in response rate between groups or no report on differences between groups	response rate < 65%; response rate not reported
	deduct 1 point from 3 or 2 if description of non-responders missing		
3. Design - course of measurement		prospective	retrospective
4. Design - informants		multi-informants (on psychological/ behavioural adjustment and/ or quality of life; medical assessment **not** included)	single informant
5. Design - controls		control group and/ or healthy norm comparison	neither controls nor normative data
6. Outcome Assessment	standardised, validated measures (e.g. CBCL, YSR)	non-validated method, i.e. self made questionnaires or translation of questionnaires yet psychometric evaluation	non-validated method, i.e. self made questionnaires or translation of questionnaires yet no further evaluation
7. Statistical data analyses – test assumptions		test assumptions considered (e.g. transformation of skewed values, non-parametric tests)	test assumptions violated
8. Statistical data analyses – type-I error		type-I error correction	no consideration of type-I error
9. Confounding and effect modification	basic medical and sociodemographic variables were adjusted for	basic medical and sociodemographic variables were considered	no information on confounding factors given
score per column			
overall score			

Figure A.2: Systematic review: Criteria for methodological quality of included studies

Appendix B

Parental comments

Following discharge of their child from hospital after open-heart surgery, parents answered open questions in addition to the standardised questionnaires. Exemplary, some answers are presented here:

1. What stressed you the most in relation to the heart surgery of your child during the last weeks?

Reactions of my child

- To see my child in pain
- His state after surgery
- My terrified daughter, who sometimes cried with panic (traumatisation?)
- The traumatisation of my child by hospitalisation. How will she cope?

Loss of parental role

- The inability to bring about relief for him
- Leaving my child with strangers
- The fact that there was nothing I could do
- The long time during which I could not have any physical contact with my daughter
- To give away responsibility
- Saying good bye before surgery

Worries

- Thoughts relating to the surgery's failure
- The fear to lose him. The fear of complications
- Not knowing whether everything will be alright after surgery
- Not knowing whether our daughter will be able to cope with everything positively
- Fear of lasting brain damage
- Insecurity
- Administering medications myself at home at the right time

- Fear of additional diagnoses
- How will my child develop after surgery? Will she be the same?
- Was our decision right, to have the surgery done?
- I get very anxious when she coughs or shows any sign of illness
- Fear that he will suffer
- Thoughts about the next surgery

Feelings of guilt

- Self blame, that he is ill at all
- To make my healthy looking child undergo heart surgery

Siblings

- My daughter has to go through this, too. She is very anxious
- I have hardly had any time left for my older son
- My older child copes badly with the situation and needs a lot of attention
- Having to leave my daughter with her grandparents
- My six-year old daughter is very anxious and behaves jealous. She is very clingy with us. She fears that we might forget about her.

Parental exhaustion

- No time for recovery during the hospitalisation of my son. Suppression of my own needs.
- Always when you think it can only get better, there comes worse.
- Lack of time and sleep

Organisational issues during hospitalisation

- Getting everything organised: Visits in hospital, job, household, caring for the other children
- Having to function despite all the fears and worries
- The never ending bureaucracy
- The whole new situation (unfamiliar people, building)
- Who is with my big family (6 children) when I am with my son in hospital?
- How are we to cope financially?
- Inability to plan the near future.

Miscellaneous

- My lack of knowledge
- I have to constantly remind her not to jump around while her brother is allowed to do so

- To see other children who are in a worse state than my child
- To experience the fate of the other children with CHD
- Where is the justice? Why can my child not have any more luck?

2. During the last weeks, what helped you the most in coping with the illness and the treatment of your child?

Contact with the child

- To be with my child, being able to do something
- To see my child fighting with great strength
- The friendly smile of my daughter when she sees us, when we can speak and play with her

Social contacts

- My partner, my children, my parents, knowing that we, somehow, will go through this together
- The positive attitude of my husband
- Empathy and support by my friends
- To have contact with other affected families
- Getting the chance to talk about it at any time with my family, friends and medical personnel
- Patience, understanding, and clear answers by staff
- Talking to affected parents via the Association of Parents of Children with CHD

Trust

- I felt my son was in good hands
- Competency of the doctors and care staff who always kept us informed well
- Honesty
- Getting to know the surgeon and liking him
- To experience the good care and seeing that everybody gives their best
- Being allowed to cry

Information

- A report on television about heart surgery in children
- Talking to the heart surgeon
- Explanations by medical staff, paediatricians, cardiologists
- Books, experiences shared via the internet

- Detailed and honest information about the illness and surgery by everybody involved

Coping

- Seeking distraction
- The belief in God and His wisdom
- Homoeopathic remedies
- Time off from hospital taking a rest in the sun
- Trying to live an as normal life as possible, in particular for the siblings
- Feeling hope

3. What kind of additional support would you have wished for during and/or after the hospitalisation of your child?

Structural support during hospitalisation

- That my partner had stayed with me in hospital overnight
- More breaks and cover at the bedsite
- Informal meetings of affected mothers, for instance drinking coffee together
- More privacy, single rooms for children
- More room on the ward
- Kindergarten for siblings all day including Saturdays and Sundays
- It would have been great to have had a bedstead next to my newborn child, sitting on a chair was physically very hard
- More comfortable chairs after Caesarean cut

Financial support during hospitalisation

- Paid holidays
- Household support
- Financial cover of food and travel costs

Professional support during hospitalisation

- Psychological support
- More medical details by physicians
- More regular medical updates, particularly in the evenings
- Continual information on the medical progress of my child
- If someone had offered me a tranquillizer on the day of surgery, I would not have refused.
- More care for the parents

- None, my partner was of great help for me
- Psychological support for my older child at home
- Detailed information about array of treatment options
- More information about what to expect and what to do in the near future
- I received very good support, yet in the beginning it was too much for me to cope, too many people approached me
- All necessary support needed I received from my family and friends
- More continuity with primary carers
- Everything the hospital could do for us was done. Thank you very much.
- I don't know what could have made the situation any better

Professional support after discharge

- Following the good support in hospital, help with medical needs of the child at home is urgently needed
- Help with behavioural difficulties of my operated son (sleeping difficulties) and his sister (very demanding, anxious to be alone, jealous)
- Suddenly everything went so fast, my son was discharged and I was very anxious of the responsibility

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Zürich, April 2006

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